Hepatic Sinusoidal Obstruction Syndrome Induced by Non-transplant Chemotherapy for Non-Hodgkin Lymphoma

Miho Sakamura¹, Kazuto Tajiri¹, Shigeharu Miwa², Kohei Nagata¹, Kengo Kawai¹, Takayoshi Miyazono¹, Kotaro Arita¹, Akinori Wada¹, Jun Murakami¹ and Toshiro Sugiyama¹

Abstract

Hepatic sinusoidal obstruction syndrome (SOS), a serious complication that mainly occurs after hematopoietic-stem cell transplantation (HSCT), is caused by damage to the sinusoidal endothelial cells after the obstruction of the sinusoid. Recently, hepatic SOS was reported to occur after non-HSCT chemotherapies. This report describes a patient who experienced hepatic SOS after non-HSCT chemotherapy for non-Hodgkin lymphoma. A liver biopsy showed the slight dilatation of the hepatic sinusoid, which may be indicative of hepatic SOS. Hepatic SOS should be included in the differential diagnosis of patients with severe liver injury following the administration of chemotherapy regimens that are toxic to the vascular endothelial cells.

Key words: sinusoidal obstruction syndrome, chemotherapy, cyclophosphamide, jaundice, drug-induced liver injury

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Introduction

Hepatic sinusoidal obstruction syndrome (SOS), also known as veno-occlusive disease (VOD), is a serious, life-threatening complication that is sometimes observed after hematopoietic-stem cell transplantation (HSCT) (1, 2). Pathophysiologically, SOS results from the activation of the sinusoidal endothelial cells (SECs), leading to the damage of these cells and the obstruction of the hepatic sinusoids in the acinar zone 3 (3). SECs are activated by chemotherapy and radiotherapy, resulting in the sustained and intense production of cytokines, which induces endothelial damage and sinusoidal endothelial swelling (3). The progression of SOS involves the depletion of glutathione and nitric oxide from the SECs, the increased expression of intrahepatic matrix metalloproteinases and vascular endothelial growth factor, and the activation of clotting factors (4). These alterations induce the egress of red blood cells, leucocytes and cellular debris into the space of Disse, leading to the obstruction of the sinusoid (1).

Recently, SOS has been reported to be induced by processes other than HSCT. For example, patients with metastatic colorectal cancer who receive oxaliplatin-based neo-adjuvant chemotherapy frequently experience SOS, resulting from toxic injury to the SECs (5). Moreover, a significant correlation was observed between the administration of oxaliplatin and the development of SOS, suggesting the importance of the functional liver reserve in patients undergoing major heptectomy for colorectal metastasis (6). These reports suggested that chemotherapies that are toxic to endothelial cells may induce SOS, especially in patients with liver damage.

We herein describe the case of a patient who developed hepatic SOS after non-HSCT chemotherapy for non-Hodgkin lymphoma. SOS should be considered in patients with refractory liver injury after chemotherapy.

Case Report

The patient was a 58-year-old Japanese man who had previously undergone splenectomy with red blood cell transfusion for autoimmune hemolytic anemia. Prior to his presentation at our hospital, he had experienced a fever of 38°C,
night sweats, and fatigue for several days. At admission, he had systemic lymphadenopathy. The laboratory data showed a white blood cell count of 9,100/μL with normal fractions, hemoglobin, 10.7 g/dL, lactate dehydrogenase (LDH) 470 U/L, and soluble interleukin-2 receptor 6,188 U/L. The patient’s liver enzyme levels were within normal limits, and he was negative for hepatitis B surface antigen, anti-hepatitis C virus (HCV) antibody, and anti-human immunodeficiency virus antibody. Serum antibodies to Epstein-Barr virus (EBV) demonstrated a past infection pattern. An esophagogastroduodenal endoscopy showed an irregular ulcer in the body of the stomach and multiple flat-elevated lesions in the duodenum (Fig. 1A and B). Biopsies of these lesions (<4 - <6 in Fig. 1A and <1 - <2 in Fig. 1B) revealed diffuse large B cell lymphoma (DLBCL). Computed tomography (CT) showed multiple adenopathy of the lymph nodes of the neck, axilla, mesentery, and paraaorta (Fig. 1C-E), with the uptake of fluorodeoxyglucose. Following a cervical lymph node biopsy, he was diagnosed with a stage IVB DLBCL.

The patient was started on treatment for DLBCL, which consisted of rituximab, cyclophosphamide (CPA), doxorubicin (DXR), vincristine (VCR) and prednisolone (R-CHOP). The treatment reduced his body temperature and serum LDH concentration (Fig. 2A). However, fluorescence in situ hybridization revealed that his lymphoma tissue was positive for both MYC and BCL2 rearrangements. Thus, he was re-diagnosed with double-hit lymphoma (DHL), an aggressive disease that is associated with poor clinical outcomes (7). Although R-CHOP has been associated with inferior outcomes in patients with DHL (7), at the present time, there is no standard treatment for DHL. Data from retrospective studies suggest that more intensive chemotherapy, such as R-CODOX-M/IVAC, which consists of rituximab, CPA, VCR, DXR and methotrexate (R-CODOX-M) alternated by ifosfamide, etoposide and high-dose cytarabine (IVAC), may achieve better outcomes in patients with DHL (8). After 2 cycles of R-CHOP, he was started on R-CODOX-M/IVAC. After the first cycle of R-CODOX-M, the patient’s hepatobiliary enzyme levels were transiently elevated, dropping to normal levels in the absence of treatment. His hepatobiliary enzyme levels were elevated again after the second cycle of R-CODOX-M/IVAC (Fig. 2A); for example, the concentrations of aspartate aminotransferase (AST) and alanine aminotransferase (ALT) were 516 IU/L and 288 IU/L, respectively, and the concentrations of total and direct bilirubin were 5.5 mg/dL and 3.9 mg/dL, respectively. A blood test revealed a white blood cell count of 800/μL, a hemoglobin level of 6.3 g/dL and a platelet count of 3,000/μL because of the myelosuppressive effect of the chemotherapy. A physical examination showed body weight gain (+2 kg/week), jaundice, lower leg edema and abdominal distention. However he did not complain about abdominal pain. The patient remained negative for hepatitis B virus (HBV)-DNA and antibodies to HCV. Serum antibodies to herpes simplex virus, cytomegalovirus (CMV) and EBV indicated their past infection. Although the serum transaminase concentration was slightly decreased without any specific treatment, the serum bilirubin concentration gradually increased. Abdominal ultrasonography showed a normal hepatobiliary tract.
with hepatomegaly and mild ascites on the surface of the liver. These findings were suggestive of severe drug-induced liver injury; thus, all possibly causative drugs, including the antibiotics that were initiated after admission, were discontinued. Nevertheless, the serum concentrations of liver enzymes remained high. The bilirubin level to rise until it peaked at 34.4 mg/dL (Fig. 2A). CT showed hepatomegaly with a geographic low density area at the posterior segment of the liver (Fig. 2B). A liver biopsy specimen showed bile congestion of the bile capillaries and hepatocytes, as well as sinusoidal dilation, but the structure of the bile duct was preserved and there was no evidence of central vein stenosis or obstruction (Fig. 3). The patient was therefore diagnosed with severe cholestatic-type drug-induced liver injury. He was treated with nafamostat mesilate in addition to glycyr rhizic acid and ursodeoxycholic acid and was observed carefully. However, his severe jaundice persisted and his liver function did not recover. Follow-up CT showed progressive atrophy of the liver and an increase in ascites (Fig. 2C-E), followed by CMV pneumonia. Despite being admitted to the intensive care unit and receiving ventilator support, there was an exacerbation of the patient’s pneumonia and he died of respiratory failure.

An autopsy was performed. His liver weighted 1,175 g, and its surface division resembled nutmeg liver (Fig. 4A). Microscopically, torn hepatic cords were visible, along with fibrosis of the sinusoids, bile congestion, and stenosis of the central vein. The latter finding is considered to be a characteristic of hepatic SOS (Fig. 4B-F). Inflammatory cell infiltration was less apparent, and there was no evidence of thrombosis. We also observed congestion of the central vein due to the occlusion of venules, ischemic necrosis of the hepatocytes, the growth of connective tissue under SECs by the dilatation of the sinusoids, along with the narrowing and occlusion of the sinusoids (Fig. 4B-F). Based on these findings, this patient was diagnosed with hepatic SOS. The autopsy also revealed that there were no identifiable lymphoma cells in any of the organs or lymph nodes.

**Discussion**

Hepatic SOS is a life-threatening complication that is usually observed after HSCT; however, some patients experience hepatic SOS outside the transplantation setting (4). Clinical diagnostic criteria have been proposed for the diagnosis of hepatic SOS (9, 10). These are based on the presence of the following clinical findings within the first three weeks after HSCT: 1) jaundice (bilirubin >2 mg/dL); 2) hepatomegaly or right upper quadrant pain; and 3) weight gain (11). In hepatic SOS, the liver histology shows dilatation of the sinusoids, centrlobular congestion or hemorrhagic necrosis. Non-thrombotic fibrous occlusion of the terminal hepatic vein is a characteristic finding of hepatic SOS (4). In this case, SOS had been suspected due to jaundice, ascites and body weight gain; however, the diagnosis of SOS was not confirmed by liver biopsy findings. Liver
hepatic SOS and the failure to recognize the centrilobular biopsies are almost never obtained during the acute phase of connective tissue.

**Figure 3.** The liver biopsy results. A) Hematoxylin and Eosin (H&E) staining (×20). Hepatocellular necrosis was not observed in the lobular and perportal area. B) H&E staining (×400). The arrow represents a bile plug. C) H&E staining (×100). The arrow represents a preserved bile duct. Mild inflammation was observed in the portal area. D) H&E staining (×20) showing congestion in the parenchymal area. E) H&E staining (×200) the arrowhead shows dilatation of the sinusoid and congestion caused by erythrocytes. F) Azan-Mallory staining (×400). The arrow represents the central vein which shows no venular occlusion.

**Figure 4.** The pathological findings of the liver at autopsy. A) The macroscopic findings of the liver. Congestion and cholestasis are found. B) H&E staining (×400) showing the dilation of the sinusoid due to erythrocytes (arrowhead) and a bile plug (arrow). C) Azan staining (×400) showing the growth of connective tissue under the sinusoidal endothelial cells (arrowhead). D) H&E stainingg (×20) showing the congestion of the parenchyma. E) H&E staining (×400) showing stenosis of the central vein (arrowhead) and ischemic necrosis of the hepatocytes. F) Azan staining (×400) showing the deposition of connective tissue around the central vein, which caused stenosis of the central vein (arrowhead). CV: central vein

venopathy may lead to the misinterpretation of the histologic findings (4). Thus, clinicians should carefully con-
sider the possibility of hepatic SOS if clinical manifestations indicating hepatic SOS are observed after chemotherapy.

The risk factors for SOS include older age, female gender, specific types of conditioning regimen (e.g. myeloablative), preexisting liver diseases, ATIII defects, and thalassemia (4). In particular, patients with a serum transaminase level of >2.5 times the upper limit of normal (ULN), a serum bilirubin level of >1.5 times the ULN, liver cirrhosis, hepatic irradiation, and active viral hepatitits are considered to be at risk of SOS (12, 13). The previous use of hepatotoxic drugs is also a risk factor (4). This patient experienced a serum transaminase concentration of 10 times the ULN after the first cycle of R-CODOX, suggesting that this treatment regimen may have been responsible for the induction of hepatic SOS.

The drugs administered to our patient may have also influenced liver dysfunction leading to hepatic SOS. The intensity of the transplant conditioning regimen has been reported to be the greatest risk factor for SOS (14). In R-CODOX-M/IVAC, the dose of CPA is higher than in other regimens. For example, in R-CHOP for DLBCL, the dose of CPA is 750 mg/m² (15). In contrast, in R-CODOX-M/IVAC for DHL, the dose of CPA is 1,600 mg/m² (8), or approximately two-fold higher. Furthermore, CPA itself is hepatotoxic. CPA metabolites have been shown to deplete hepatic glutathione levels, inducing oxidative stress and hepatotoxicity (16), which may lead to SOS. Genetic polymorphisms of glutathione S-transferase (GST) M1, which are associated with glutathione depletion have recently been shown to be a risk factor for the development of SOS in patients undergoing HSCT and those receiving oxaliplatin-based chemotherapy (17, 18). Although we could not investigate the presence of possible genetic polymorphisms of GST M1 in our patient, caution should be exercised in treating patients with high-dose CPA or chemotherapy regimens that contain agents that are toxic to the SECs.

Despite our best efforts, we did not reach the diagnosis of SOS while the patient was alive. Although we performed a liver biopsy to assess the cause of liver injury, the liver parenchyma showed only sinusoidal dilatation and congestion. The absence of sinusoidal obstruction or central vein stenosis in the biopsy specimen prevented us from reaching a diagnosis of hepatic SOS while the patient was alive. A liver biopsy is essential in diagnosing liver injury; however biopsy samples are limited, as they only evaluate 0.002% of the area of the liver (19). CT findings, such as hepateomegaly, abdominal effusion and geographic low density changes, have been recently reported as characteristics of hepatic SOS (20). Although additional patients with hepatic SOS should be assessed by CT, hepatic SOS should be considered when CT shows hepateomegaly, abdominal effusion and a geographic low density area or when a liver biopsy shows sinusoidal dilatation and congestion after the administration of a chemotherapy regimen that is toxic to the SECs.

Hepatic SOS is usually treated symptomatically. There are no established therapies for this condition other than for defibrotide (DF), a polydisperse mixture of single-stranded oligonucleotides with antithrombotic and fibrinolytic effects (2, 14). DF has been shown to be effective both in the treatment of severe SOS accompanied by multiple organ failure (21, 22), and in preventing the development of SOS (23). Although the patient of the present study may have benefited from DF, this agent has not yet been approved in Japan. Clinical trials of DF are currently ongoing in Japan.

Hepatic SOS occurs in patients after HSCT and in those receiving chemotherapy regimens that are especially toxic to the SECs. Identifying patients who are at risk of developing SOS, and the awareness of the possibility of SOS in patients who experience refractory liver injury after chemotherapy are important. CT findings, such as hepatomegaly, abdominal effusion and geographic low density changes, and liver biopsy findings, such as sinusoidal dilatation and congestion, that occur after chemotherapy should be considered to be highly suggestive of hepatic SOS.

The authors state that they have no Conflict of Interest (COI).

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