

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

Miho Sakumura¹, 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

(Intern Med 56: 395-400, 2017)

(DOI: 10.2169/internalmedicine.56.7669)

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 proc-

esses other than HSCT. For example, patients with metastatic colorectal cancer who receive oxaliplatin-based neoadjuvant 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 hepatectomy 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,

¹The Third Department of Internal Medicine, Toyama University Hospital, Japan and ²Diagnostic Pathology, Faculty of Medicine, University of Toyama, Japan

Received for publication May 2, 2016; Accepted for publication June 14, 2016

Correspondence to Dr. Kazuto Tajiri, tajikazu@med.u-toyama.ac.jp

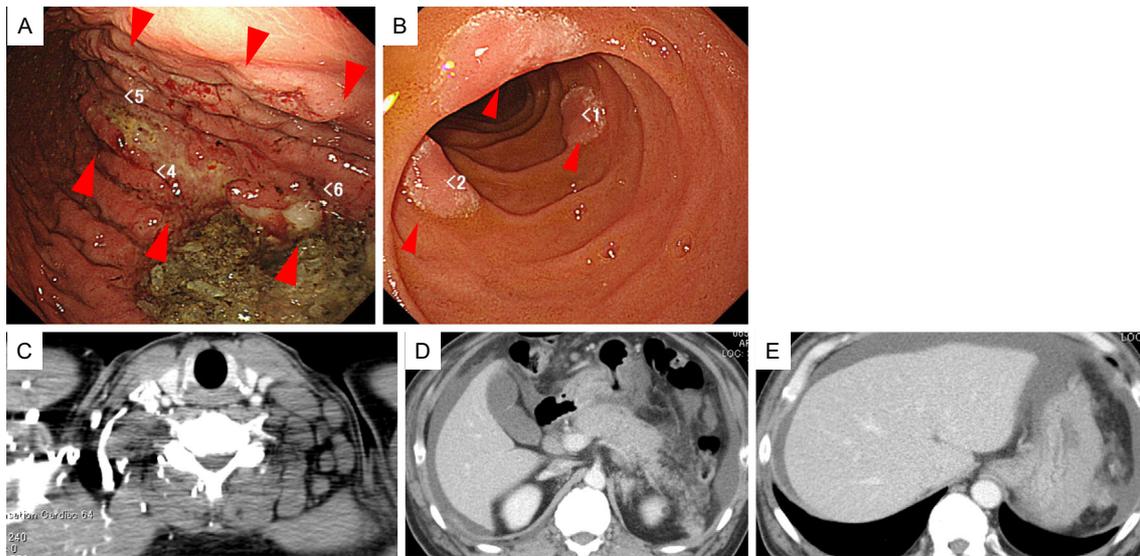


Figure 1. A)-B) The esophagogastroduodenoscopy findings. A) The stomach. The red arrowheads indicate irregular ulcer lesions in the body of the stomach. B) The duodenum. The red arrowheads indicate multiple flat elevations in the second portion of the duodenum. Biopsies were performed from <1-<2 and <4-<6, and all of the samples revealed diffuse large B-cell lymphoma. C)-E) The contrast-enhanced computed tomography findings. C) A CT image showing the enlargement of multiple lymph nodes from the neck. D) A CT image showing a thickened gastric wall caused by lymphomatous lesion. E) A CT image showing the ascites on the surface of the liver. A cytological analysis of the ascites revealed class V.

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/ μ L 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 out-

comes 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/ μ L, a hemoglobin level of 6.3 g/dL and a platelet count of 3,000/ μ L 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

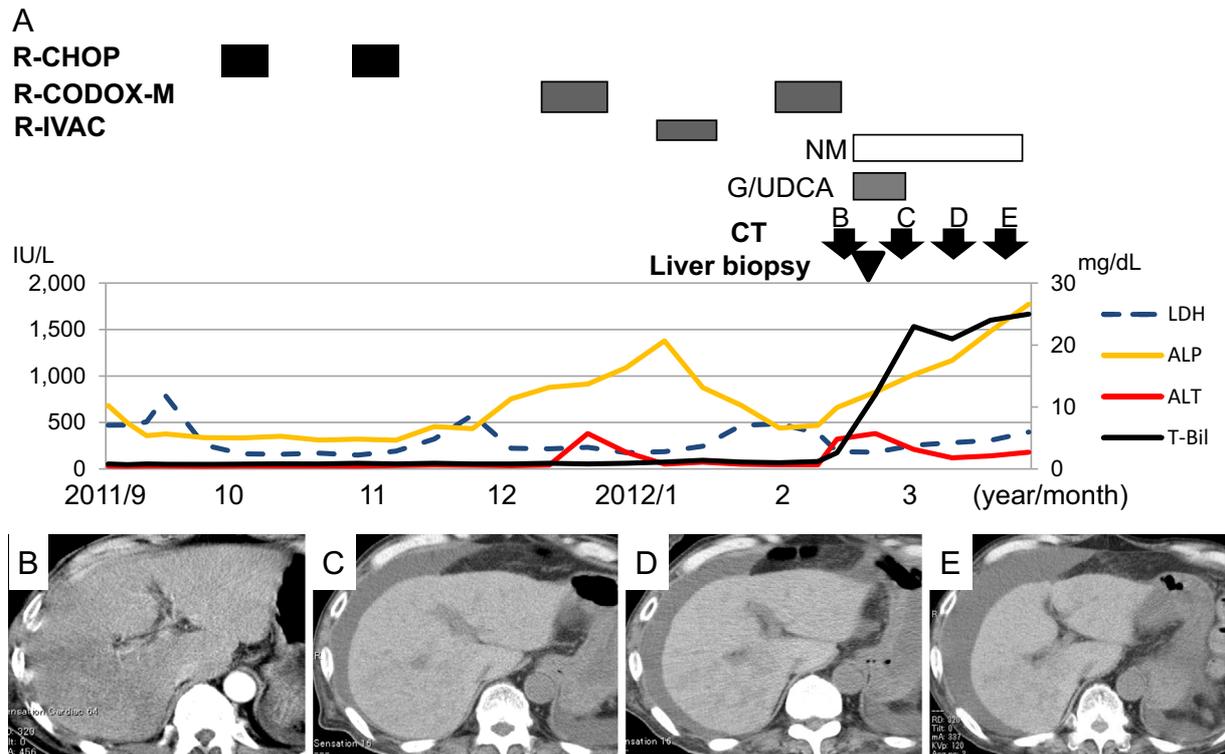


Figure 2. A) The clinical course of the present patient, including the timing of CT (as shown as B-E). NM: nafamostat mesilate, G: glycyrrhizic acid, UDCA: ursodeoxycholic acid. B) A contrast-enhanced CT image shows hepatomegaly and geographic low density area at the posterior segment of the liver. C)-E) CT images showing the increase of ascites and the progression of liver atrophy.

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 dilatation, 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 glycyrrhizic 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 charac-

teristic 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, centrilobular 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

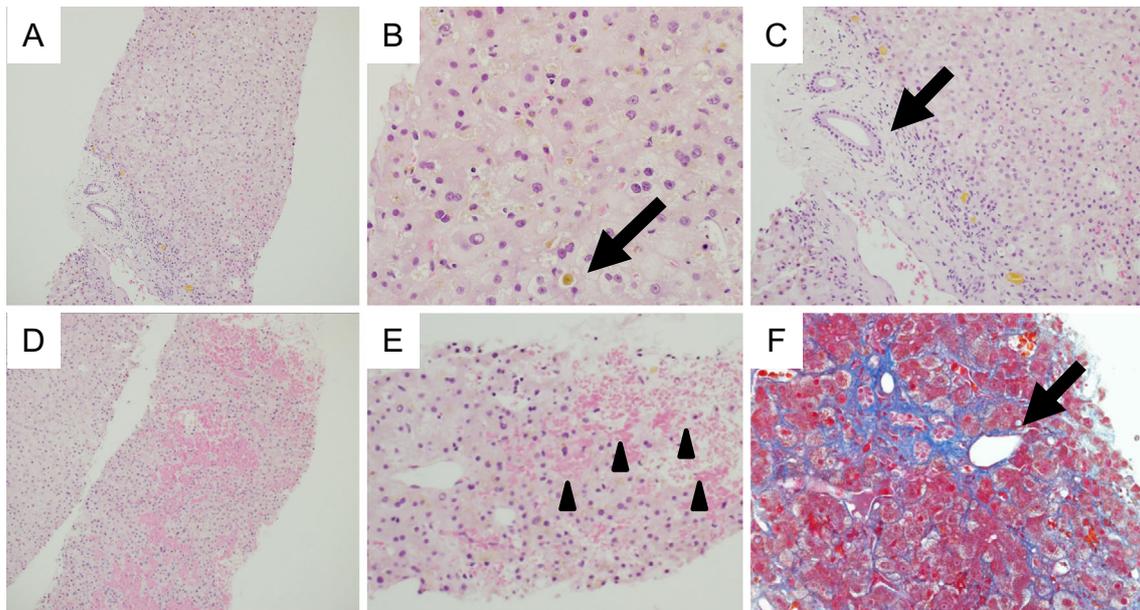


Figure 3. The liver biopsy results. A) Hematoxylin and Eosin (H&E) staining ($\times 20$). Hepatocellular necrosis was not observed in the lobular and periportal area. B) H&E staining ($\times 400$). The arrow represents a bile plug. C) H&E staining ($\times 100$). The arrow represents a preserved bile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

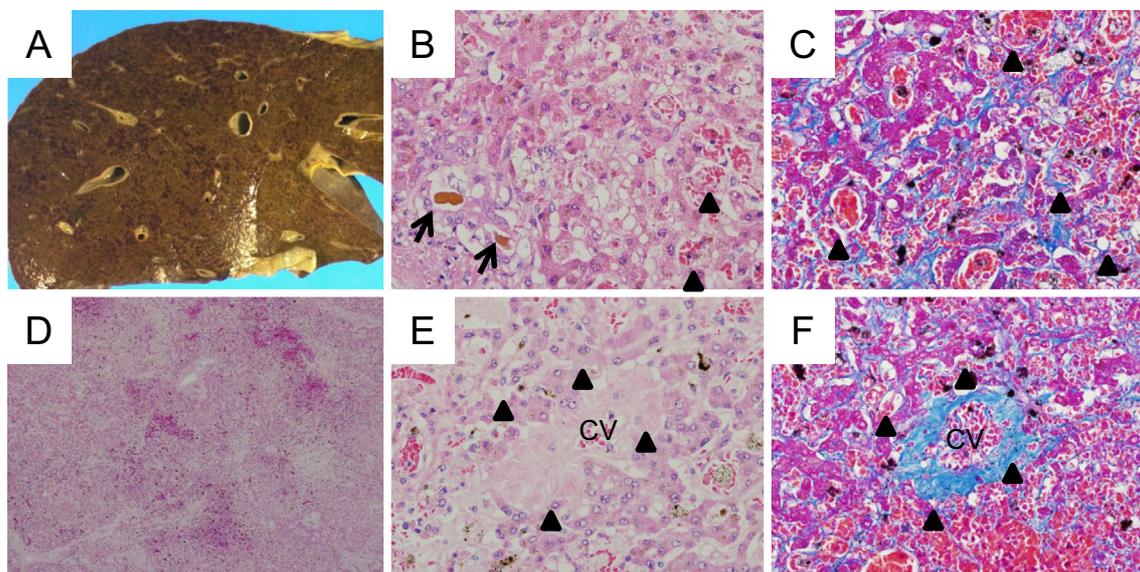


Figure 4. The pathological findings of the liver at autopsy. A) The macroscopic findings of the liver. Congestion and cholestasis are found. B) H&E staining ($\times 400$) showing the dilation of the sinusoid due to erythrocytes (arrowhead) and a bile plug (arrow). C) Azan staining ($\times 400$) showing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

biopsies are almost never obtained during the acute phase of 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 hepatitis 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 hepatomegaly, 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 hepatomegaly, 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).

References

1. Carreras E. Venocclusive disease of the liver after hemopoietic cell transplantation. *Eur J Haematol* **64**: 281-291, 2000.
2. Mohty M, Malard F, Abecassis M, et al. Sinusoidal obstruction syndrome/veno-occlusive disease: current situation and perspectives—a position statement from the European Society for Blood and Marrow Transplantation (EBMT). *Bone Marrow Transplant* **50**: 781-789, 2015.
3. Carreras E, Diaz-Ricart M. The role of the endothelium in the short-term complications of hematopoietic SCT. *Bone Marrow Transplant* **46**: 1495-1502, 2011.
4. Fan CQ, Crawford JM. Sinusoidal obstruction syndrome (hepatic veno-occlusive disease). *J Clin Exp Hepatol* **4**: 332-346, 2014.
5. Rubbia-Brandt L, Audard V, Sartoretti P, et al. Severe hepatic sinusoidal obstruction associated with oxaliplatin-based chemotherapy in patients with metastatic colorectal cancer. *Ann Oncol* **15**: 460-466, 2004.
6. Robinson SM, Wilson CH, Burt AD, Manas DM, White SA. Chemotherapy-associated liver injury in patients with colorectal liver metastases: a systematic review and meta-analysis. *Ann Surg Oncol* **19**: 4287-4299, 2012.
7. Petrich AM, Nabhan C, Smith SM. MYC-associated and double-hit lymphomas: a review of pathobiology, prognosis, and therapeutic approaches. *Cancer* **120**: 3884-3895, 2014.
8. Mead GM, Sydes MR, Walewski J, et al. An international evaluation of CODOX-M and CODOX-M alternating with IVAC in adult Burkitt's lymphoma: results of United Kingdom Lymphoma Group LY06 study. *Ann Oncol* **13**: 1264-1274, 2002.
9. McDonald GB, Sharma P, Matthews DE, Shulman HM, Thomas ED. Venocclusive disease of the liver after bone marrow transplantation: diagnosis, incidence, and predisposing factors. *Hepatology* **4**: 116-122, 1984.
10. Jones RJ, Lee KS, Beschoner WE, et al. Venocclusive disease of the liver following bone marrow transplantation. *Transplantation* **44**: 778-783, 1987.
11. Dignan FL, Wynn RF, Hadzic N, et al. BCSH/BSBMT guideline: diagnosis and management of veno-occlusive disease (sinusoidal

- obstruction syndrome) following haematopoietic stem cell transplantation. *Br J Haematol* **163**: 444-457, 2013.
12. Carreras E, Bertz H, Arcese W, et al. Incidence and outcome of hepatic veno-occlusive disease after blood or marrow transplantation: a prospective cohort study of the European Group for Blood and Marrow Transplantation. European Group for Blood and Marrow Transplantation Chronic Leukemia Working Party. *Blood* **92**: 3599-3604, 1998.
 13. McDonald GB, Hinds MS, Fisher LD, et al. Veno-occlusive disease of the liver and multiorgan failure after bone marrow transplantation: a cohort study of 355 patients. *Ann Intern Med* **118**: 255-267, 1993.
 14. Ho VT, Revta C, Richardson PG. Hepatic veno-occlusive disease after hematopoietic stem cell transplantation: update on defibrotide and other current investigational therapies. *Bone Marrow Transplant* **41**: 229-237, 2008.
 15. Coiffier B, Lepage E, Briere J, et al. CHOP chemotherapy plus rituximab compared with CHOP alone in elderly patients with diffuse large-B-cell lymphoma. *N Engl J Med* **346**: 235-242, 2002.
 16. DeLeve LD. Cellular target of cyclophosphamide toxicity in the murine liver: role of glutathione and site of metabolic activation. *Hepatology* **24**: 830-837, 1996.
 17. Srivastava A, Poonkuzhali B, Shaji RV, et al. Glutathione S-transferase M1 polymorphism: a risk factor for hepatic venoocclusive disease in bone marrow transplantation. *Blood* **104**: 1574-1577, 2004.
 18. Vreuls CP, Olde Damink SW, Koek GH, et al. Glutathione S-transferase M1-null genotype as risk factor for SOS in oxaliplatin-treated patients with metastatic colorectal cancer. *Br J Cancer* **108**: 676-680, 2013.
 19. Rockey DC, Caldwell SH, Goodman ZD, et al. Liver biopsy. *Hepatology* **49**: 1017-1044, 2009.
 20. Shao H, Chen HZ, Zhu JS, et al. Computed tomography findings of hepatic veno-occlusive disease caused by Sedum aizoon with histopathological correlation. *Braz J Med Biol Res* **48**: 1145-1150, 2015.
 21. Richardson PG, Soiffer RJ, Antin JH, et al. Defibrotide for the treatment of severe hepatic veno-occlusive disease and multiorgan failure after stem cell transplantation: a multicenter, randomized, dose-finding trial. *Biol Blood Marrow Transplant* **16**: 1005-1017, 2010.
 22. Richardson PG, Elias AD, Krishnan A, et al. Treatment of severe veno-occlusive disease with defibrotide: compassionate use results in response without significant toxicity in a high-risk population. *Blood* **92**: 737-744, 1998.
 23. Corbacioglu S, Cesaro S, Faraci M, et al. Defibrotide for prophylaxis of hepatic veno-occlusive disease in paediatric haemopoietic stem-cell transplantation: an open-label, phase 3, randomised controlled trial. *Lancet* **379**: 1301-1309, 2012.

The Internal Medicine is an Open Access article distributed under the Creative Commons Attribution-NonCommercial-NoDerivatives 4.0 International License. To view the details of this license, please visit (<https://creativecommons.org/licenses/by-nc-nd/4.0/>).