INTRODUCTION

Drug-induced liver injury presents with extremely diverse histologic patterns, including necroinflammatory, cholestatic, steatotic and vascular patterns. Sinusoidal obstruction syndrome (SOS), also referred to as toxic sinusoidal injury, veno-occlusive disease or “blue liver syndrome”, is a commonly recognized vascular pattern of drug-induced liver injury, and has been frequently associated with oxaliplatin-based chemotherapy. In this issue, we present a case of SOS after 6 cycles of oxaliplatin-based preoperative chemotherapy for colorectal cancer liver metastasis and discuss the morphologic findings of SOS.

CASE SUMMARY

A 58-year-old Korean woman presented with hematochezia during 2 months in June, 2011. She had no significant past medical history and also denied any previous intake of alcohol, smoking and herbal agents. The initial computed tomography (CT) scan demonstrated two masses in the rectum and ascending colon, multiple enlarged regional lymph nodes, two metastatic nodules in segments 6 and 8 of the liver and also pulmonary metastasis. She was treated with 6 cycles of XELOX (oral capecitabine [1,000 mg/m² twice daily on days 1 to 14] plus oxaliplatin [130 mg/m² on day 1]) over a 5-month period. A follow-up CT scan at 5 months after chemotherapy revealed a partial tumor response, and after one month, she underwent low anterior resection of the rectum, right hemihepatectomy of the liver, and left lobectomy of the lung. Preoperative liver function tests were within normal limits: aspartate aminotransferase (AST) 24 IU/L, alanine aminotransferase (ALT) 12 IU/L, alkaline phosphatase (ALP) 60 IU/L, total bilirubin 0.8 mg/dL, and prothrombin time (PT) 1.07 INR. Serologic tests for hepatitis B and hepatitis C virus were negative.

PATHOLOGIC FINDINGS

On gross examination, the resected liver showed 2 yellowish-white nodules corresponding to the metastatic lesions, and the background liver showed a distinct mottled appearance, with areas of congestion alternating with relatively normal-appearing hepatic parenchyme (Fig. 1). Microscopically, the nodules were consistent with metastatic adenocarcinomas from the colorectum. The non-tumorous liver parenchyme showed diffuse sinusoidal dilatation and congestion with extravasation of red blood cells, which

Abbreviations:
PEL, Parenchymal extinction lesion; SOS, sinusoidal obstruction syndrome

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Figure 1. Macroscopic finding of sinusoidal obstruction syndrome. The non-neoplastic hepatic parenchyma is diffusely mottled, with geographic areas of congestion alternating with relatively normal-appearing liver.

Figure 2. Representative microscopic findings of sinusoidal obstruction syndrome (A-D). Patchy perivenular sinusoidal dilatation and congestion with hepatocyte plate disruption (A ×100 magnification). Approximation of portal structures and hepatic vein with loss of intervening hepatocytes, and perivenular and perisinusoidal fibrosis (B ×100 magnification, Masson’s trichrome stain). Sinusoidal dilatation and congestion with atrophy and disruption of hepatocyte plates (C ×200 magnification). An obliterated terminal hepatic venule is seen in the center (arrow). Masson’s trichrome stain demonstrating fibrous obliteration of a terminal hepatic venule (D ×400 magnification).
predominantly affected the centrilobular zones. Hepatic cytotic plate
disruption was seen in areas of severe sinusoidal congestion, and
parenchymal extinction lesions (PELs) – defined as the approxima-
tion of hepatic vein remnants and portal tracts with loss of inter-
vening hepatocytes – were noted. Masson’s trichrome stain high-
lighted centrilobular venular fibrosis and perisinusoidal fibrosis,
and fibrous occlusion of small terminal hepatic venules was seen
(Fig. 2). Macrovesicular and microvesicular steatosis was seen in
less than 33% of hepatocytes. Hepatocellular ballooning was not
prominent, and there was no significant lobular or portal inflam-
mation. There was no significant cholestasis or ductular reaction.

DISCUSSION

Oxaliplatin-based chemotherapeutic regimens such as FOLFOX
(5-fluorouracil (5-FU), leucovorin and oxaliplatin) and XELOX
(capcitabine and oxaliplatin) are commonly used for patients with
colorectal cancer liver metastases – preoperative chemotherapy
has been shown to reduce the size of the hepatic metastases, sub-
sequently rendering the tumor more amenable to curative resec-
tion. However, while these drugs have demonstrated impressive
results in the treatment of colorectal cancers, they have also been
associated with various degrees of hepatotoxicity. 5-FU has been
associated with hepatic steatosis, possibly mediated by excessive
production of reactive oxygen species resulting in the accumula-
tion of lipid vesicles in hepatocytes, and an association be-
 tween irinotecan and steatohepatitis has been reported. Oxali-
platin has been frequently associated with SOS. SOS has been
described in association with drugs including oxaliplatin, azathio-
prine, cyteasimine, dacarbazine, daclomycin, carmustine (BCNU),
6-mercaptopurine, 6-thioguanine, busulfan, dimethyl busulfan,
cytosine arabinoside, cyclophosphamide, indinomycin-N-oxide, mus-
tine-HCl, doxorubicin, urethane, vincristine, mitomycin-C, etopo-
side, arsenic, thorium dioxide (Thorotrast), and intraarterial fluoro-
deoxycyuridine. SOS related to oxaliplatin administration was first
described by Rubbia-Brandt et al, and is characterized by the fol-
lowing histologic findings: sinusoidal dilatation and congestion,
centrilobular vein fibrosis and obstruction, perisinusoidal fibrosis,
necrosis of pericentral hepatocytes, PELs, hepatocyte plate disrup-
tion, and nodular regenerative hyperplasia. These changes are
generally irregularly distributed within the hepatic paren-
chyme; however, if the changes are more extensive it is possible to
recognize SOS on gross examination, where the liver appears dif-
sely “nodular” due to alternating areas of congestion/hemor-
rhage with relatively normal-looking areas.

Although the pathogenesis of chemotherapy-induced SOS is still
unclear, it has been suggested that initial toxic damage to sinusoi-
dal endothelial cells results in the disruption of the sinusoidal wall,
resulting in marked sinusoidal dilatation and extravasation of
erthrocytes into the Disse’s spaces through the discontinuities in
the endothelial lining. In addition, activation of hepatic stellate
cells results in the deposition of collagen matrix in the perisinusoi-
dal spaces and centrilobular vein. The degree of SOS has been
suggested to be time-and dose-dependent- the extent of sinusoi-
dal dilatation has been shown to be significantly higher in livers
exposed to higher numbers of chemotherapy cycles. Interest-
ingly, Overman et al. demonstrated that oxaliplatin-increased
SOS was associated with portal hypertension, splenomegaly and
subsequent thrombocytopenia, and suggested that increased
spleen size could correlate with increasing grade of hepatic sinusoi-
dal injury.

The relationship between preoperative chemotherapy-related
liver pathology and postoperative outcome is still controversial.
Some studies have demonstrated a lack of significant association
between chemotherapy-associated hepatopathy and postopera-
tive outcome. On the other hand, preoperative chemotherapy
was significantly correlated with increased postoperative morbidity
and abnormal liver function tests such as AST, ALT, and total bili-
rubin in another recent study, suggesting that preoperative che-
motherapy may lead to some derangement of liver function. There
is limited data regarding the postoperative outcome in rela-
tion to SOS following oxaliplatin-based treatment, but an associa-
tion between the presence of SOS and increased postoperative
morbidity has been suggested: sinusoidal injury has been associ-
ated with a significantly higher complication rate and poorer liver
functional reserve among patients undergoing a major hepatec-
tomy, suggesting the importance of careful surgical candidate selec-
tion in patients previously exposed to oxaliplatin-based treat-
ment.

Conflicts of Interest

The authors have no conflicts to disclose.

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