Case Report

DOI: 10.7860/JCDR/2018/30409.11086

Internal Medicine Section

Reversible Sinusoidal Obstruction Syndrome with Nodular Regenerative Hyperplasia Following Oxaliplatin-Based Chemotherapy

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ABSTRACT

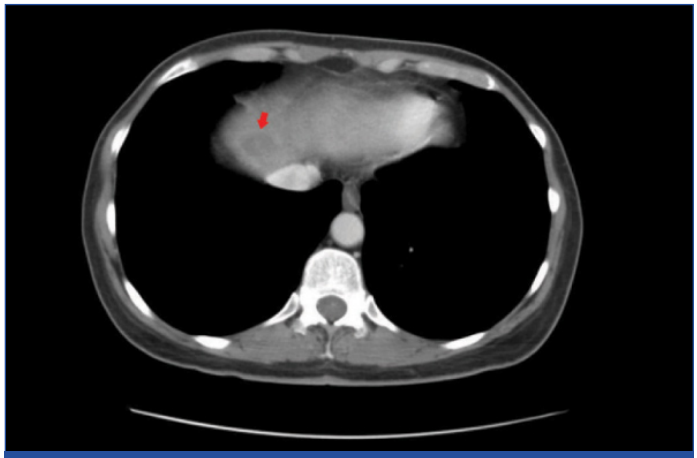
Sinusoidal Obstruction Syndrome (SOS) is a form of hepatic injury characterized by damage to small hepatic vessels resulting in occlusion of the terminal hepatic venules and hepatic sinusoids. Oxaliplatin has been associated with distinct side effects; one of them reported recently which is SOS. We report a patient with history of colon cancer who presented with elevated liver enzymes and liver nodules. After extensive evaluation, the patient found to have a severe form of SOS which is the Nodular Regenerative Hyperplasia (NRH) as a result of oxaliplatin based chemotherapy. We also report the reversibility of this condition after treatment cessation which is something that is not always feasible. The diagnosis of this case was challenging as the liver nodules thought to be metastases initially and that is why we believe recognizing this entity is crucial to prevent misdiagnosis and consequent unnecessary surgical intervention.

Keywords: Colon cancer, Oxaliplatin, Drug-induced liver injury

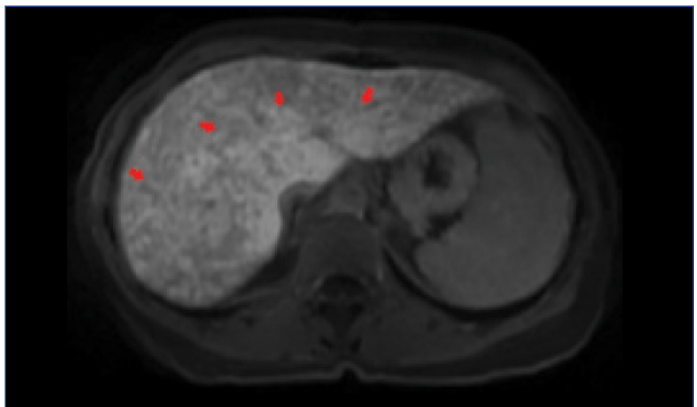
CASE REPORT

A 61-year-old female with a history of stage IIIB (pT3, pN1b, cM0) adenocarcinoma of the colon after post-laparoscopic-assisted resection of the sigmoid and left colon. She was started on adjuvant chemotherapy with oxaliplatin and capecitabine. Two months later, she was found to have elevated liver enzymes. Her Alanine Aminotransferase (ALT) was 71 U/L, Aspartate Aminotransferase (AST) was 80 U/L, and Alkaline Phosphatase (ALP) was 134 U/L. Her vital signs were normal and on her physical examination there were no signs of liver disease. Computed Tomography (CT) of the abdomen showed multiple linear nodular hypo densities within the liver, most noticeable on the delayed images along with hypodensity within the dome of the liver, suggesting metastasis [Table/Fig-1]. These findings were not present in the CT scan done prior to chemotherapy initiation. Because the lesions were seen only on the delayed images of CT abdomen, the liver biopsy was done which showed mild steatosis with no significant fibrosis as the nodular lesions were probably missed in non-contrast CT guided biopsy.

The patient then underwent Magnetic Resonance Imaging (MRI) of the abdomen [Table/Fig-2] with Gadoxetate disodium (Eovist®) which showed a linear, nodular, patchy low signal throughout the liver consistent with sinusoidal obstruction syndrome and nodular regenerative hyperplasia concerning for oxaliplatin toxicity and so it was stopped. Three months later, a follow-up MRI of the abdomen [Table/Fig-3] showed significant improvement in the previously noted diffuse liver disease with improvement in liver enzymes [Table/Fig-4].



[Table/Fig-1]: CT scan showing hypodensity within the dome of the liver (Red Arrow).

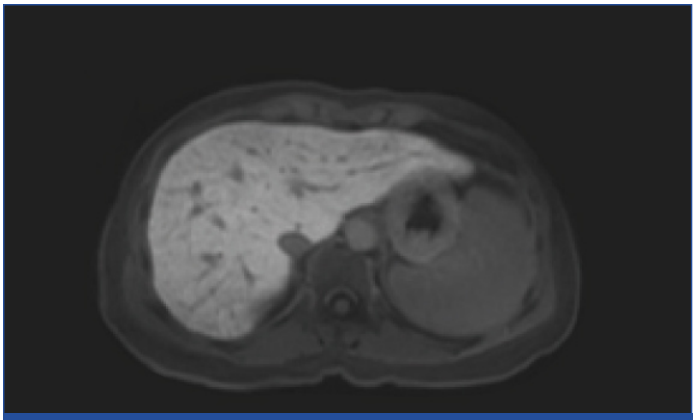


[Table/Fig-2]: Liver MRI showing the linear, nodular low signal throughout the liver (Red Arrows), consistent with sinusoidal obstruction syndrome due to Oxaliplatin therapy.

DISCUSSION

Oxaliplatin-based chemotherapy is most commonly used in the setting of colorectal cancer and its associated metastatic disease [1]. In patients with colorectal hepatic metastasis, oxaliplatin increases the surgical amenability of the formerly unresectable lesions, subsequently increasing the disease-free survival and overall survival rates [2]. However, liver injury, including SOS, has been observed after chemotherapy that utilizes oxaliplatin with the incidence rate of sinusoidal changes reaching up to 75% [3]. SOS has also been described in association with other drugs such as azathioprine, 6-mercaptopurine, 6-thioguanine, busulfan, cyclophosphamide, doxorubicin, etoposide, etc., [4].

Since the first clinical study describing this entity in 2004 [5],



[Table/Fig-3]: Liver MRI showing significant improvement in the previously noted diffuse liver disease.

oxaliplatin-induced hepatic injury has become a major concern because its pattern mimics metastatic liver lesions in imaging, leading to misdiagnosis and overtreatment. Indeed, there are three reported cases of focal SOS similar to our case and have been treated by surgical resection [6-8]. The exact mechanism of liver injury due to oxaliplatin is not fully understood. However, oxaliplatin is more toxic to sinusoidal endothelial cells than hepatocytes. Other forms of oxaliplatin-related liver damage are centrilobular, perisinusoidal, and venular fibrosis; peliosis; and NRH [9]. NRH is characterized by the diffuse transformation of normal hepatic parenchyma into small, regenerative nodules and represents the most significant degree of injury in SOS. While the pathogenesis of NRH is not clear, it has been suggested that it represents a chronic ischemic injury secondary to disturbance to the blood flow within the liver, which consequently results in portal hypertension [10].

	Initial Values	Oxaliplatin Stopped	After 2 months	After 6 Months
ALP (38-126 U/L)	134	119	129	126
ALT (11-66 U/L)	71	26	25	46
AST (14-59 U/L)	80	42	34	55

[Table/Fig-4]: Demonstrates the patient's liver enzymes trend over the period from starting of the Oxaliplatin therapy until 6 months after it was stopped.

SOS, previously termed veno-occlusive disease, or blue liver syndrome is a distinctive and potentially fatal form of hepatic injury that occurs predominantly after drug exposure. The characteristic histological features of SOS are sinusoidal congestion and dilatation; disruption of the sinusoidal membrane and collagen deposition within the perisinusoidal space, leading to a bluish appearance of the liver [5]. Clinically, oxaliplatin-induced SOS symptoms are nonspecific. Elevated transaminase levels, jaundice, hepatomegaly, splenomegaly with subsequent thrombocytopenia and ascites could occur. Moreover, it may be associated with an increased perioperative morbidity and bleeding risk as well as delayed liver regeneration after liver resection [11]. A diagnosis of SOS can often be made based on clinical presentation and imaging studies. A liver biopsy is diagnostic but not always practical due to chemotherapy-induced thrombocytopenia and neutropenia. Gadolinium-Ethoxybenzyl magnetic resonance imaging (Gd-EOB MRI), which is the most reliable modality in colorectal liver metastasis, shows a defect in the hepatocyte phase in SOS similar to imaging findings of colorectal liver metastasis. Therefore, a qualitative imaging modality such as diffusion-weighted MRI may be superior because the cellular density is higher in cancer than in SOS [12]. Also, the reticular hypointensity in hepatobiliary phase images of Gd-EOB MRI is highly specific for SOS and it can be divided into five levels with levels four and five considered indicating SOS [13]. Additionally, SOS does not show uptake in a Positron Emission Tomography (PET) scan, whereas 90-94% of liver metastases are detected with PET/CT scans [14].

Management of SOS is aimed to avoid further injury caused by oxaliplatin; preventing unnecessary complications such as hypotension, electrolyte and acid-base imbalance, renal and pulmonary failure, infectious complications and maintaining intravascular volume and renal perfusion while limiting third-space fluid accumulation. Glutamine (or glutathione) has been investigated as a potential therapy for oxaliplatin-induced liver injury [15]. Further, the incidence and severity of sinusoidal changes have been shown to be reduced with co-administration of Bevacizumab [16].

Regarding the reversibility of SOS, our case demonstrated a good response after cessation of the oxaliplatin therapy with disappearance of MRI liver changes and normalization of liver enzyme level. However, this is not always the case as the persistence and even the progression of SOS and NRH have been observed in the short and long term [17]. It is certain that the risk of progressive disease is undeniable, especially in patients exposed to higher numbers of chemotherapy cycles.

CONCLUSION

Oxaliplatin-induced liver injury should be considered in patients presenting with liver nodules who were previously treated with chemotherapy regimen containing oxaliplatin. We recommend that the appropriate imaging should be performed in order to differentiate this entity from metastasis so that unnecessary surgical intervention and overtreatment can be minimized.

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FINANCIAL OR OTHER COMPETING INTERESTS: None.

Date of Submission: **May 26, 2017**
Date of Peer Review: **Aug 09, 2017**
Date of Acceptance: **Sep 16, 2017**
Date of Publishing: **Jan 01, 2018**