

April 20, 2022

Dear Editor,



Please find enclosed the edited manuscript in Word format (file name: 74504_Auto_Edited.doc).

Title: Isolated gastric varices bleeding related to non-cirrhotic portal hypertension following oxaliplatin-based chemotherapy: A case report

Author: Xu Zhang, Yan Ying Gao, De Zhao Song, and Bao Xin Qian

Name of Journal: *World Journal of Gastroenterology*

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The manuscript has been improved according to the suggestions of reviewers:

1 Format has been updated

2 Revision has been made according to the suggestions of the reviewer

The first review's composition comment on the manuscript and my answer

Well presented and interesting case report. The presented data should raise awareness of the rare presenting complication of the oxaliplatin-based chemotherapy.

Answer: Thank you for your recognition of this case report. We will improve the deficiencies.

The second review's composition comment on the manuscript and my answer

It is an interesting paper on a topic not well known. It is necessary to deepen the work and better detail the points below:

1) define better the toxicity as Hepatic sinusoidal obstruction syndrome (SOS) is an obliterative venulitis of the terminal hepatic venules, which in its more severe forms imparts a high risk of mortality. SOS, also known as veno-occlusive disease (VOD), occurs as a result of cytoreductive therapy prior to hematopoietic stem cell transplantation (HSCT), following oxaliplatin-containing adjuvant or neoadjuvant chemotherapy for colorectal carcinoma metastatic to the liver and treated by partial hepatectomy

Answer: Yes, we agree with your comment and add the related contents of SOS.

2) since in China it is common and usual the use of herbal medicine specify if the patient has taken pyrrolizidine alkaloid-containing herbal remedies

Answer: Yes, we agree with your comment and emphasize the medication history of the patient in discussion.

3) if the patient has other particular settings such as the autosomal recessive condition of veno-occlusive disease with immunodeficiency (VODI).

Answer: Yes, we appreciate with your comment and make the corresponding supplements in the personal and family history. Hepatic Veno-occlusive disease with immunodeficiency (VODI) is a serious form of combined immune deficiency, which is difficult to treat and often fatal. A few cases have been reported. Most of the patients have serious complications in infancy. In this case, the patient had no known history of liver disease, the isolated gastric varices bleeding appeared after eight cycles of oxaliplatin combined with capecitabine. Preoperative gastroscopy did not show any abnormalities. Therefore, the liver damage and gastric varices were considered to be directly related to oxaliplatin-containing chemotherapy.

4) does it exist a central pathogenic event is toxic destruction of hepatic sinusoidal endothelial cells, with sloughing and downstream occlusion of terminal hepatic venules?

Answer: Yes, we agree with your comment and make the corresponding explanation about this part. The typical SOS manifestations such as intrasinusoidal hemorrhage, thrombosis, and obstruction were not seen in pathological examination, similar to a few case reports. The pathophysiological process that causes NCPH, considering the previous reports, it is believed to be secondary to the sinusoidal damage. Some literature reported that SOS may resolve within 9 months. Therefore, it was suspected that the sinusoidal damage had gradually recovered after chemotherapy termination.

5) Does it exist other contributing factors as SEC glutathione depletion, nitric oxide depletion, increased intrahepatic expression of matrix metalloproteinases and vascular endothelial growth factor (VEGF), and activation of clotting factors?

Answer: Yes, we agree with your comment and make the corresponding explanation about the mechanism by which oxaliplatin causes hepatic sinusoidal injury.

6) Is present the clinical presentation of SOS includes jaundice, development of right upper-quadrant pain and tender hepatomegaly, ascites, and unexplained weight gain?

Answer: Yes, we thank for your comment and make the corresponding explanation about this part in the discussion. There was no typical clinical and pathological presentation of SOS present on our patient. We speculated the sinusoidal damage in this patient was mild, not enough to cause typical clinical presentations of SOS.

7) Owing to the potentially critical condition of these patients, have you thought about performing transjugular biopsy may be the preferred route for liver biopsy to exclude other potential causes of liver dysfunction and to establish a diagnosis of SOS?

Answer: Yes, we agree with your comment. Gastric varices do exist. Thus, the diagnosis was questionable. A liver biopsy was necessary to establish a definitive diagnosis. Transjugular liver biopsy is a highly efficacious, well-tolerated, and safe procedure. So transjugular liver biopsy was performed, and meanwhile the hepatic venous pressure gradient (HVPG) was measured.

The third review's composition comment on the manuscript and my answer

1. "pt4n2mx" should be written pT4N2Mx to avoid confusion.

Answer: I'm sorry the standard terminology has not been used and we make the corresponding modification.

2. It is unclear if the patient had splenomegaly or not. Throughout a lot of the manuscript it is stated she did not. However the CT scan reported "slightly enlarged spleen". Which is it?

Answer: The enhanced computed tomography (CT) scan of the abdomen and pelvis showed the outer edge of spleen is slightly larger than 5 rib units, with a length of 12.6cm and a thickness of 4.8cm, which support spleen enlargement was slight. Meanwhile, no significant enlargement of the spleen was detected on palpation. Therefore "no obvious splenomegaly" was stated in discussion.

3. When the authors write "Gastroscopy showed severe isolated gastric varices in the fundus"- what does severe entail? Were they actively bleeding? Did they have stigmata of recent haemorrhage? "

Answer: Yes, we agree with your comment and make the corresponding modification about the description of gastric varices according to grading standards of esophageal and gastric varices of Japan 2010.

4. "False flocculus structure" is not a term that is used in the English language histological vocabulary. Can the authors please use more orthodox terminology to describe the presence or absence of cirrhosis? There are several instances where the term "hepatic hepatic sinuses" is used erroneously. "Dysimmunity" is also not an English language term.

Answer: Yes, we agree with your comment, "False flocculus structure" is revised to "pseudolobuli formation", "hepatic hepatic sinuses" is a writing error and revised to "hepatic sinusoids", "Dysimmunity" is revised to "immune disorders".

5. It is stated in the discussion that the patient had "spleno-renal shunting". However this is never mentioned in the case report.

Answer: Yes, the enhanced computed tomography (CT) scan of the abdomen and pelvis showed varices in the gastric fundus with "gastro-renal shunting". "spleno-renal shunting" in the discussion is a writing error and has been corrected.

6. There should be more discussion about the patient's clinical presentation. Was she having haematemesis or melena? What dose of octreotide, what sort of proton pump inhibitors, how much blood transfusion did she receive? What were her vital signs?

Answer: Yes, I agree with your comment and make the corresponding supplements in the part of chief complaints, physical examination and treatment.

7. Similarly there should be more discussion about the treatment of the patient after gastroscopy. Was she commenced on beta blockers? Did she stay in hospital for several days afterward? Were further gastroscopies performed in an outpatient setting?

Answer: Yes, I agree with your comment and make the corresponding supplements in the outcome and follow-up.

The fourth review's composition comment on the manuscript and my answer

I had the opportunity to review a paper "Isolated gastric varices bleeding related to non-cirrhotic portal hypertension following oxaliplatin-based chemotherapy: A case report", and I found very interesting. There is no problem to publish the manuscript.

Answer: Thank you for your recognition of this case report. We will improve the deficiencies.