

Dear Editor,

We are resubmitting the Manuscript ID: 42652 entitled Duodenal Variceal Bleeding Secondary to IPH Treated With TIPS Plus Embolization: A Case Report and Literature Review to World Journal of Clinical Cases. We thank the reviewers for their insightful and helpful comments and questions.

We have revised the manuscript and specific responses to reviewer's comments are outlined below. We have used the "TRACK CHANGES" function of MICROSOFT WORD to make it easy to review all the manuscript changes. If you do not like the "track changes" format, please simply select "Accept changes" to get rid of the TRACK markers. The authors thank you for your time and consideration, and we look forward to your response soon.

Sincerely yours

GuiHai Guo

**Reviewer 1:**

The authors have described an usual case of bleeding secondary to duodenal varices treated with TIPS. The case is well explained. Perhaps you can consider a shorter version of discussion.

**Response:**As per your suggestion, we have modified, and made the discussion section shorter.

**Reviewer 2:**

This case report is interesting and quite well documented and presented. However, some rare cause of portal hypertension are not mentioned as excluded in the case of this patient. These are: Biliary diseases (seronegative PBC, small duct PSC, toxic biliary injury e.g. from vinyl chloride), granulomatous liver lesions (e.g. schistosomiasis, mineral oil granuloma, sarcoidosis), fibrosis of the space of Disse due to metabolic (e.g. nonalcoholic fatty liver disease, Zellweger syndrome), drug/toxin-induced (e.g. amiodarone, methotrexate, alcohol, vinyl chloride, copper). Was amyloid or light-chain deposition in the space of Disse excluded? Were Gaucher

disease or agnogenic myeloid metaplasia excluded? Were veno occlusive diseases, granulomatous phlebitis (e.g. from sarcoidosis, Mycobacterium avium or M. intracellulare infection) or lipogranulomas excluded?

**Response:** Indeed, some rare cause of portal hypertension as suggested by reviewer are not mentioned as excluded in the case of this patient. Thank you for your suggestion. We have checked medical records seriously, asked the pathologists to re-examine the liver pathological tissue sections, and contacted the patient to learn more about medical history.

**1) Biliary diseases (seronegative PBC, small duct PSC, toxic biliary injury e.g. from vinyl chloride):** Initially, the serological test of autoimmune hepatic disease was negative. Subsequently, The liver biopsy is re-examined by the pathologists, and the hepatic pathological manifestations do not support biliary diseases such as seronegative PBC, small duct PSC, toxic biliary injury e.g. from vinyl chloride. These biliary diseases can be ruled out.

**2) granulomatous liver lesions (e.g. schistosomiasis, mineral oil granuloma, sarcoidosis):** The liver biopsy is re-examined by the pathologists, and granulomatous liver lesions including schistosomiasis, mineral oil granuloma, sarcoidosis are not shown in hepatic sections. In addition, she denied the history of Schistosomiasis exposure as mentioned. Therefore, granulomatous liver lesions (e.g. schistosomiasis, mineral oil granuloma, sarcoidosis) can be ruled out.

**3) fibrosis of the space of Disse due to metabolic (e.g. nonalcoholic fatty liver disease, Zellweger syndrome):** ①The patient denied metabolic history, such as obesity, metabolic syndrome, and Type 2 diabetes. The further examination on liver by CT and ultrasound was normal, and the pathological appearance of nonalcoholic fatty liver disease was not observed by the pathologists. Thus, nonalcoholic fatty liver disease can be excluded as mentioned. ②The signs and symptoms of Zellweger syndrome typically appear during the newborn period and may include poor muscle tone (hypotonia), poor feeding, seizures, hearing loss, vision loss, distinctive facial features, and skeletal abnormalities. The history of this case was 2 years, and the patient denied the above symptoms. Although there is no genetic test, a critical examination for diagnosis, Zellweger syndrome can be excluded due to no signs of Zellweger syndrome in the pathological sections after review by the pathologists.

**4) drug/toxin-induced (e.g. amiodarone, methotrexate, alcohol, vinyl chloride, copper):** The patient denied the exposure history of drug or toxin such as amiodarone, methotrexate, alcohol (as mentioned), vinyl chloride, copper. Thus, these drug/toxin-induced liver diseases can be ruled out.

**5) Was amyloid or light-chain deposition in the space of Disse excluded?:** Amyloid or light-chain deposition in liver are associated with increased ALP, hepatomegaly, and nephrotic syndrome, which is commonly the local manifestation of systemic syndrome. The liver is usually involved in association with renal lesions. Isolated liver involvement has been rarely reported. The serological examination of renal function and ALP was normal, and normal liver size was detected by an enhanced CT scan as mentioned. Although deficiency of PAS and Congo red staining in liver sections, the hepatic pathological manifestation of amyloid or light-chain deposition is not found by the pathologists after re-examination.

**6) Were Gaucher disease or agnogenic myeloid metaplasia excluded?:** ① **Gaucher disease:** A diagnosis of Gaucher disease is suspected in individuals who have bone problems, enlarged liver and spleen (hepatosplenomegaly), changes in red blood cell levels, easy bleeding and bruising from low platelets or signs of nervous system problems. The final diagnosis of Gaucher disease is dependent on measuring the activity level of the enzyme glucocerebrosidase or analyzing the GBA gene for the four most common GBA mutations. The liver biopsy is re-examined, and the pathological appearance of liver involvement in Gaucher disease is not detected by the pathologists. Although deficiency of genetic test and enzymatic detection, Gaucher disease can be ruled out. ② **agnogenic myeloid metaplasia:** agnogenic myeloid metaplasia is usually secondary to chronic granulocytic leukemia. Marrow examination is an essential diagnostic procedure for the disease. In this case, the appearance of agnogenic myeloid metaplasia was not shown in bone marrow aspiration.

**7) Were veno occlusive diseases, granulomatous phlebitis (e.g. from sarcoidosis, Mycobacterium avium or M. intracellulare infection) or lipogranulomas excluded?:** ① **veno occlusive diseases:** Veno-occlusive disease (VOD), which is also called sinusoidal obstruction syndrome (SOS), happens when the small blood vessels that lead into the liver and are inside the liver become blocked. VOD is caused by high doses of chemotherapy and radiation therapy given before an allogeneic stem cell transplant. It develops in the first few

weeks after a stem cell transplant and can be mild to severe. As for the patient, she denied the history of stem cell transplant. In addition, the pathological appearance of VOD is not found by the pathologists after re-examination. Thus, VOD can be ruled out.②Granulomatous phlebitis and lipogranulomas are not observed in the liver sections by the pathologists after re-examination, and thus these diseases can be excluded.

**Reviewer 3:**

1. This is a case report. Please add more details of the pathophysiology of duodenal variceal bleeding secondary to IPH.

**Response:** We have added some details about the pathophysiology of duodenal variceal bleeding secondary to IPH, please see the revised third paragraph of discussion section.

2. What is the new knowledge from this report? Finally, please recommend the readers “How to apply this knowledge for routine clinical practice?”.

**Response:1)New knowledge from this report:** TIPS plus embolization may be more appropriate to control the rupture or reduce the risk of bleeding of the giant duodenal varices.

**2)Recommendation in routine clinical practice:**In routine clinical practice, we recommend that TIPS plus embolization with coils and histoacryl is a good option for large ectopic varices.

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**We have highlighted in the updated version of the manuscript.** The authors thank you for your time and consideration, and we look forward to your response soon.

Sincerely yours

GuiHai Guo

**1. A short running title of less than 6 words should be provided.**

**Response: We have provided it.**

**2. The approved grant application form(s) will be released online together with the manuscript in order for readers to obtain more information about the study and to increase the likelihood of subsequent citation.** Our purpose of publishing the approved grant application form(s) is to promote efficient academic communication, accelerate scientific progress in the related field, and improve productive sharing of research ideas. In addition, a copy of the full approved grant application form(s), consisting of the information section and body section, should be provided to the BPG in PDF format.

**Response: We have provided it.**

**3. In order to improve the quality of Case Report manuscripts, authors should download and complete the ‘CARE Checklist (2016) of information to include when writing a case report’ to ensure that the manuscript meets the requirements of the CARE Checklist (2016). Authors must state on the title page of the manuscript that the guidelines of the CARE Checklist (2016) have been adopted (see below). Authors must upload the PDF version of the completed checklist to the system.**

**Response: We have provided it.**

**4. An informative, structured abstract of no less than 250 words should accompany each manuscript. Abstract should include background, case summary, and conclusion.** The Abstract will be structured into the following sections, adhering to the word count thresholds indicated in parentheses:

BACKGROUND (no more than 80 words)

*What does this case report add to the medical literature? Why did you write it up?*

CASE SUMMARY (no more than 150 words)

*Chief complaints, diagnoses, interventions, and outcomes.*

CONCLUSION (no more than 20 words)

*What is the main “take-away” lesson from this case?*

**Response: We have revised it as your suggestion.**

**5. Please offer the audio core tip, the requirement are as follows:**

**In order to attract readers to read your full-text article, we request that the first author make an audio file describing your final core tip. This audio file will be published online, along with your article. Please submit audio files according to the following specifications:**

**Acceptable file formats:** .mp3, .wav, or .aiff

**Maximum file size:** 10 MB

To achieve the best quality, when saving audio files as an mp3, use a setting of 256 kbps or higher for stereo or 128 kbps or higher for mono. Sampling rate should be

either 44.1 kHz or 48 kHz. Bit rate should be either 16 or 24 bit. To avoid audible clipping noise, please make sure that audio levels do not exceed 0 dBFS.

**Response: We have provided it before.**

**6.The main text contains introduction, introduction, case presentation, multidisciplinary expert consultation, final diagnosis, treatment, outcome and follow-up, discussion, experiences and lessons, acknowledgments, and references. The main text writing is as follows:**

#### INTRODUCTION

The current standard of care and contributions of this case—with references (1-2 paragraphs)

CASE PRESENTATION (should include chief complaints, history of present illness, history of past illness, physical examination, laboratory testing, imaging examination, and genetic testing, *etc.*)

*Chief complaints*

*History of present illness*

*History of past illness*

*Physical examination*

*Laboratory testing*

*Imaging examination*

*Genetic testing*

...

#### MULTIDISCIPLINARY EXPERT CONSULTATION (If relevant)

*Andrzej S Tarnawski, DSc, MD, PhD, Professor, Chief Gastroenterology*

...

*Bao-Gan Peng, MD, PhD, Chief Doctor, Professor, Department of Spinal Surgery*

...

#### FINAL DIAGNOSIS

#### TREATMENT

#### OUTCOME AND FOLLOW-UP

#### DISCUSSION

- (1) Strengths and limitations in your approach to this case;
- (2) Specify how this case report informs practice or Clinical Practice Guidelines;
- (3) How does this case report suggest a testable hypothesis? ; and
- (4) Conclusions and rationale.

#### EXPERIENCES AND LESSONS (3 to 5 bullet points – this is a required field)

**Response: We have revised it as your suggestion.**