

Dear editor and reviewers,

Thank you very much for your letter and advice concerning our manuscript entitled "Spontaneous acute epidural hematoma secondary to skull and dural metastasis of hepatocellular carcinoma: A case report and literature review" (Manuscript NO.: 76385, Case Report). Those comments are valuable and helpful for revising and improving our paper, as well as the important guiding significance to our researches. We do appreciate you for giving us the opportunity to revise our manuscript. According to your suggestion, we rephrased the manuscript from the patient's medical history to post-operative outcome and follow-ups, instead of brain metastases, we compared the incidence of skull metastasis of HCC with the other bone metastasis. Now we would like to re-submit our manuscript for your consideration. We have addressed the comments raised by the reviewers, and the amendments are highlighted in red in the revised manuscript. These changes will not influence the content and framework of the paper. Point by point responses to the reviewers' comments are listed below this letter.

We appreciate the editors/reviewers' warm work earnestly, and hope that the revised version of the manuscript will meet with approval.

I look forward to hearing from you soon.

Best wishes!

Sincerely yours,

Yong Yang, MD, PhD

We would like to express our sincere thanks to the reviewers for the constructive comments.

Replies to Reviewers and Editor

Reviewer #1:

Specific Comments to Authors: Lv et al. reported a case of acute epidural hematoma due to metastatic HCC to the skull bone. They conducted a literature review to delineate the clinical pictures and outcomes of such disease presentation.

1. It was not clear the status of HBV infection. How about the HBsAg, HBeAg and HBV DNA in this patient? Had the patient received antiviral agents for HBV? Was the patient cirrhotic or not? If yes, how about the Child-Pugh score or MELD score for the patient?

Response:

The results of HBsAg, HBeAg and HBV DNA were supplemented in the section of laboratory examinations. Please refer to page 4 line 6 to 16.

The patient did not take regular antiviral therapy as prescribed by the doctor. Please refer to page 3 line 14-15.

The patient was confirmed cirrhosis 6 months before AEDH and the Child-Pugh score of this patient is 5 (grade A) before and after TACE 6 months ago. Please refer to page 5 line 1-2.

2. How about the BCLC stage of HCC 6 months prior to the presentation of acute epidural hematoma? How about the responses of treatment after intra-arterial embolization (any imaging studies after embolization)? How about the evolution of AFP or PIVKA-II levels before and after embolization? These data should be described in details in the manuscript.

Response: The BCLC stage of this patient was (BCLC stage: B) 6 months prior to the presentation and was (BCLC stage: C) after the operation. BCLC stage progressed to D after the post-operative complications developed. The patient was diagnosed as HCC and treated with TACE in another hospital, the detailed

treatment records were unavailable. The patient did not follow the doctor's suggestion for comprehensive treatment, nor did he have regular follow-up visits to the doctors. Please refer to page 3 line 14-19.

3. Section about Laboratory examination was not acceptable. Please described in the details the laboratory results for this patient, rather to use laymen terms, such as AFP significantly elevated to ALT mildly elevated or PLT/coagulation within normal range.

Response: Thank you for your suggestion. The laboratory results were supplemented. Please refer to page 4 line 6 to 16.

4. Please make a comprehensive discussion about the overall prognosis and treatment options once the brain hemorrhage was under control. Were there any prognostic factors that predicted the overall treatment responses and overall survival? How about the role of radiotherapy for such cases? How about the role of immune check point inhibitors or tyrosine kinase inhibitors for these patients? The role of nucleos(t)ide analogues for HBV if the patients had not receive treatment.

Response: Thank you for your constructive suggestion, we made a comprehensive discussion about the overall prognosis and treatment options after the hemorrhage evacuation. Please refer to page 8 line 1 to 19.

5. Please include a reference which was not cited in the article [Delgado Maroto A, Del Moral Martínez M, Diéguez Castillo C, Casado Caballero FJ. Acute epidural haematoma as a presentation of hepatocellular carcinoma: Case report and literature review. Gastroenterol Hepatol. 2019 Mar;42(3):177-179.]

Response: Thank you for reminding us to cite this important article. We cited it in the discussion part. Please refer to page 6 line 5-6.

Reviewer #2:

Specific Comments to Authors:

1. The baseline characteristics of the patient is too simple. The initial tumor stage (BCLC or other stage), liver function (Child-Pugh score or ALBI) and tumor marker (AFP or PIVK-II) should be described.

Response: The BCLC stage of this patient was (BCLC stage: B) 6 months prior to the presentation and was (BCLC stage: C) after the operation. BCLC stage progressed to D the post-operative complications developed. The patient received TACE 6 months ago in another hospital, the detailed treatment records were unavailable. The patient did not follow the doctor's suggestion for comprehensive treatment, nor did he have regular follow-up visits to the doctors. Please refer to page 3 line 14-19.

2. Does chemotherapy used during "intra-arterial embolization"? The difference is transarterial embolization (TAE) or transcatheter arterial chemoembolization (TACE). I will recommend to use transarterial embolization (TAE) rather than intra-arterial embolization because "TAE" is a more popular term and "intra-arterial" may sometimes confused with hepatic arterial infusion chemotherapy(HAIC). 3. The follow-up status after embolization is not described. Are there any AFP, echo or CT/MRI follow-up?

Response: As the authors of this manuscript are neurosurgeons, we do agree that the term "transarterial embolization (TAE)" or "transarterial chemoembolization (TACE)" is a more formal description for the intervention procedure for this patient. In this patient, TACE was adopted in his first treatment for HCC with adriamycin and 5-fluorouracil. The patient received TACE 6 months ago in another hospital, the detailed treatment records were unavailable. The patient did not follow the doctor's suggestion for comprehensive treatment, nor did he have regular follow-up visits to the doctors.

Science editor:

1. The theme of the manuscript belongs to the scope of the journal. 2. There is no academic misconduct in the manuscript. 3. The resolution of the figure meets the requirements for publication. 4. This manuscript presents a rare case of acute epidural hematoma (AEDH) secondary to hepatocellular carcinoma (HCC) that may not have been previously reported in China, which may be of interest to readers.

5. However, the manuscript describes the following information in insufficient detail or is partially missing:

(1) The patient's current and past medical history;

Response: Thank you for your suggestion, we supplement the patient's current and past medical history. Please refer to page 3 line 8-19.

(2) The staging of HCC and the metastasis to other organs except for the skull and dura;

Response: In this patient, the BCLC staging of this patient before AEDH was B. Lung and bone metastasis were noticed in the CT scan after craniotomy procedure, which is described in the follow-up part. 10 days after the operation we re-evaluated the BCLC stage of this patient and it had progressed into BCLC stage C. BCLC stage progressed to D the post-operative complications developed. A comprehensive postoperative examination revealed that the patient had lung and bone metastases.

(3) Preoperative and postoperative laboratory test results and their changes; (4) Treatments other than dural hematoma removal surgery; (5) More importantly, the patient died 3 weeks after the operation. The authors attributed the cause of death to pulmonary infection, anemia, and liver failure, but lack corresponding evidence to support this conclusion, and the authors did not describe interventions for lung infections, anemia, and liver failure; (6) Did the patient has pulmonary infection and anemia before surgery?

Response: In the post-operative outcome and follow-up part we additionally fulfilled the post-operative description in detail, including the post-operative laboratory examination result and other supportive treatments. Pulmonary infection is an inevitable complication of patients in coma, which is why tracheotomy was performed to enable a better airway management. And the anemia and liver failure are due to the progression of HCC and cachexia due to the loss of performance status. The patient had no pulmonary infection and anemia before operation.

(7) The authors described in "Laboratory examinations" that "alanine aminotransferase was slightly elevated, and alpha-fetoprotein was significantly elevated. The platelet count and coagulation function were in the normal range", which indicated that the patient's preoperative liver damage was not severe, What causes the deterioration of the patient's liver function?

Response: Thank you for your suggestion. The laboratory results were supplemented. Please refer to page 3 line 19 to page 4 line 7. We speculate that the reasons for the rapid deterioration of liver function in this patient include: pulmonary infection secondary to postoperative coma, perioperative stress response, and the liver injury effect of drugs, the progression of HCC and the protein-energy malnutrition caused by the loss of performance status.

(8) The manuscript does not discuss the lessons to be learned from this rare case. These shortcomings of the manuscript reduce its value for publication.

Response: Thank you for your suggestion. We discussed the lessons to be learned from this rare case. Please refer to page 8 line 20 to page 9 line 2.