Dear Editors and Reviewers,

Title: Isolated hepatic tuberculosis associated with portal vein thrombosis and HBV coinfection: A case report and review of literature

Authors: Shu-Mei Zheng, Ning Lin, Shan-Hong Tang, Jia-Yi Yang, Hai-Qiong Wang, Shu-Lan Luo, Yong Zhang, Dong Mu.

Manuscript No: 69540

Thank you so much for your comments. We really appreciate your helpful advices on modifications that are valuable in improving the quality of our manuscript. The manuscript had been revised according to the comments of two reviewers and editors. Here are some explanations about changes in the manuscript.

Reviewer #1: reviewer's code: 00071178.

Specific Comments to Authors: Dear Author Thank you for this case presentation. My comment as below: In my opinion, this case is very well written. The normal limits of some blood values should be given in parentheses. It is quite interesting that this patient's PPD and ESR values were at normal levels. Because an increase in ESR values can be observed in approximately half of TB patients. It was stated that the patient was started on entecavir. however, no information was given about whether he had taken any antiviral drugs before. Has this patient been tested for HIV? Because HIV is an important risk factor for the development of extrapulmonary TB disease. Although it is not essential, I think that if a short literature review (for example, a table can be prepared) could be added to this study, it would attract more attention.

Answers for the first reviewer's comments:

1) Several normal values were added in parentheses.

2) We think that the false negative PPD result may due to the immunosuppression and malnutrition caused by the severe infection of TB. During his clinical course, ESR test was performed for several times with negative results. We think that ESR, a nonspecific indicator, may be affected by many factors, clinicians should have a comprehensive understanding and analysis of the disease.

3) The patient had never taken antiviral drugs against HBV in his medical history.

4) Upon admission, the HIV test was performed and the result was negative.

5) We added some valuable documents (reference 35-41, which are summarized in table 1) on intraabdominal TB associated with PVT to improve the quality of the manuscript.

Reviewer #2: reviewer's code: 03741771.
Specific Comments to Authors: Dear authors, great article. It was a real pleasure to read it. Please see below my specific comments: 1) please remove track changes 2) several type-setting errors. 3) Was the patient tested for HIV infection? 4) for how long anticoagulants were prescribed. Why NOAC/DOAC and not Warfarin or etc. ? Please comment 5) Why do you think PVT was secondary to TB? Please add some relevant data 6) Did the patient had intestinal TB as well? did you searched for it? Please comment 7) At this stage, the differential diagnosis of lymphoma with B symptoms was considered, It sounds quite strange. Please correct 8. Did you considered to have a biopsy from the PVT thrombus? why not? Please comment. Did the thrombus dissipated because of NOAC/DOAC therapy or due to anti TB treatment... Best wishes, TM

Answers for the second reviewer's comments:

1) All track changes had been removed.

2) Some typesetting errors had been corrected.

3) The HIV test of the patient was negative.

4) He had a total of 4 months of therapy with dabigatran. Dabigatran is a competitive, direct thrombin inhibitor. Both free and clot-bound thrombin, and thrombin-induced platelet aggregation are inhibited by the active moieties. Administration of dabigatran had several advantages over warfarin in this case. Firstly, dabigatran is not a substrate, inhibitor, or inducer of CYP450 enzymes, so it showed less drug–drug interaction than warfarin. The patient had taken four anti-TB drugs and entecavir, so we choose dabigatran as anticoagulants to prevent drug interactions. Secondly, dabigatran is eliminated primarily in the urine. Renal clearance of dabigatran is 80% of total clearance. Dabigatran is safer than warfarin in patients with hepatic impairment. Finally, INR is relatively insensitive to the exposure to dabigatran as used for warfarin monitoring, so the patient need not to monitor INR frequently when taking dabigatran.

5） We had added some clinical studies (see reference 35-41, table 1) on intraabdominal TB associated with PVT. Based on these reports, intraabdominal TB, such as peritoneum, bowel, lymph nodes, and solid organs involvements, may be associated with PVT. All the three parts of Virchow's triad: hypercoagulability, venous stasis, and endothelial dysfunction, may play a role in pathogenesis of thromboembolic complications in tuberculosis. It has been postulated that contiguous spread of inflammation, granulomas in the vessel wall with subintimal fibrosis, and intraluminal thrombi may be the other risk factors that contribute to portal thrombosis. In fact, thromboembolic complications associated with tuberculosis infection occurred in 1.5-3.4% of cases. In the present case, the most common disorders including intraabdominal carcinoma, surgery, inflammation bowl disease, and liver cirrhosis etc., which are prone to result in PVT were ruled out. The histological findings of the liver biopsy showed epithelioid granulomas with a background of caseating necrosis and acid-fast bacilli, and the therapeutic efficacy of ATT can partly interpret that the PVT may be secondary to the liver TB.

6） The patient underwent esophagogastroduodenoscopy and colonoscopy and the results were normal.

7） We had deleted the inappropriate sentences.

8） For PVT of unknown origin, a biopsy is generally recommended as the "gold standard" for definite diagnosis, but the patient refused to take a second biopsy of PVT. He would like to take the ATT and anticoagulants and monitor the improvement of clinical presentation at first, if necessary, he would undertake a PVT biopsy subsequently. Based on previous reports and our clinical experience, we think the resolution of PVT was due to both anticoagulants and ATT. First of all, anticoagulants are effective approaches to prevent propagation of the thrombus and to promote recanalization, while ATT is the most important therapy directing at the etiology to prevent thrombosis

especially at the early stage of disease.

(1) Science editor:

Issues raised: (1) The authors did not provide original pictures. Please provide the original figure documents. Please prepare and arrange the figures using PowerPoint to ensure that all graphs or arrows or text portions can be reprocessed by the editor; (2) The title is too long, and it should be no more than 18 words; And (3) The authors need to provide the original document of Signed Informed Consent Form(s).

(2) Company editor-in-chief:

Before its final acceptance, the author(s) must provide the Signed Informed Consent Form(s) or Document(s) of treatment. For example, authors from China should upload the Chinese version of the document.

Answers for the editor's comments:

1) We had prepared original pictures which can be reprocessed by the editor.

2) The revised title " Isolated hepatic tuberculosis associated with portal vein thrombosis and HBV coinfection: A case report and review of literature " is only 18 words.

3) We had provided the Chinese version of Signed Informed Consent Form.

Best regards

Yours sincerely,

Shu-Mei Zheng, Ning Lin, Shan-Hong Tang, Jia-Yi Yang, Hai-Qiong Wang, Shu-Lan Luo, Yong Zhang, Dong Mu.