

Dear Editors,

Sorry for the long wait. We thank you very much for giving us an opportunity to revise our manuscript, we appreciate editor and reviewers very much for their positive and constructive comments and suggestions on our manuscript ID "NO: 73168". Those comments are all valuable and very helpful for revising and improving our paper, as well as the important guiding significance to our researches. We have studied reviewer's comments carefully and made revision, which are marked in red in the manuscript. Please find the revised version in the attachment, which we would like to submit for your kind consideration.

We would like to express our great appreciation to you and reviewers for comments on our paper. We are looking forward to hearing from you.

Thank you and best regards.

Yours sincerely,

Ming-Li Zhu

Dear Editors and Reviewers,

Sorry for the long wait. Thank you for your letter and for the reviewers' comments concerning our manuscript ID "NO: 73168". Those comments are all valuable and very helpful for revising and improving our paper, as well as the important guiding significance to our researches. We have made correction carefully according to the comments, which we hope to meet with approval. Revised portions are marked in color in the manuscript. Corrections made to the manuscript and responds to the reviewer's comments are as follows:

Reviewer #1:

Scientific Quality: Grade C (Good)

Language Quality: Grade B (Minor language polishing)

Conclusion: Major revision

Specific Comments to Authors: In this case report, the authors tried to illustrate *M. tuberculosis* was examined by next-generation sequencing of blood samples, which was subsequently grown in conventional BacT/ALERT FA blood culture bottles through isolation from blood samples. However, there are major specific points in this manuscript as shown in following comments:

Comments 1: Regarding microbiological examination, it is recommended to add the detection of *M. tuberculosis* culture and next-generation sequencing for Pleural fluid and ascites of the patient.

Reply: Thank you very much for your comments. Blood cultured on Lowenstein-Jenden medium yielded white colonies, which were identified as *M. tuberculosis* by MALDI-TOF MS (France, Bio-Mérieux). I fully agreed with the reviewer's recommendation for next-generation sequencing of patient pleural fluid and ascites, but it was not carried out due to the high cost of next-generation sequencing.

Comments 2: The *M. tuberculosis* related factors, such as Tuberculosis spot test and Purified Protein Derivative(PPD) should be studied in this work.

Reply: Thank you very much for your comments. We strongly agreed with the reviewer and agreed that Tuberculosis spot test and Purified Protein Derivative (PPD) should be studied. However, because the patient has already been discharged from the hospital, we regretted that we cannot make up for these two experiments.

Comments 3: In the aspect of diagnosis, Is there a possibility of spontaneous bacterial peritonitis(SBP) in the patient? How to exclude the SBP?

Reply: The patient had spontaneous bacterial peritonitis (SBP). Examination of ascites fluid showed a positive Rivalta test; ascites cell counts showed 1.6×10^9 /L nucleated cells, 76% of which were neutrophils, 10% mononuclear

macrophages, 12% lymphocytes, and 2% mesothelial cells. In 2000, the consensus of the European Association For The Study Of The Liver (EASL) proposed that neutrophils $>250/\mu\text{L}$ have good sensitivity for the diagnosis of SBP. Therefore, when the number of ascites cells is more than $250/\mu\text{L}$, SBP should be considered, and empirical antibacterial therapy should be given in time^[1]. Since then, the criteria for diagnosing SBP with the number of nucleated cells in ascites $>250/\mu\text{L}$ have been used to this day. The patient has far more nucleated cells than the diagnostic criteria.

Comments 4: In the aspect of treatment, Why didn't the authors give artificial liver treatment for the Liver failure? Please give the explanation for the liver failure.

Reply: Thank you very much for your comments. The patient was not treated with artificial liver. Considering the medical expenses and prognosis, the patient and their family members refused the artificial liver treatment. He was treated with magnesium isoglycyrrhizinate for hepatoprotective therapy. The patient had a history of alcohol abuse.

HBsAb, 29.19 mIU/mL, HBcAg, 8.88 S/CO; hepatitis E antibody IgG, weakly positive, cytomegalovirus antibody IgG, positive; coxsackie virus antibody IgG, positive.

Alcohol and some of the above viruses may be factors that cause liver failure.

Comments 5: Please provide the figures of the results for the next-generation sequencing of blood samples and growth of *M. tuberculosis*.

Reply: Thank you very much for your comments. It has been modified according to the comments of the reviewer (**Figure 1** and **Figure 3**).

Reviewer #2:

Scientific Quality: Grade D (Fair)

Language Quality: Grade B (Minor language polishing)

Conclusion: Major revision

Specific Comments to Authors: This was a case report of tuberculosis bacteremia in an HIV-negative patient with liver cirrhosis. Please correct and add the following points.

Comments 1: Lung CT shows extensive lung lesions. With such extensive lung lesions, some respiratory symptoms were expected to occur. I assume that sputum culture including aspirated sputum has been done. The authors should show such results.

Reply: Thank you very much for your comments. It has been modified according to the comments of the reviewer (Line 17, Page 7). Sputum culture did not show any pathogenic bacteria.

Comments 2: What was the life history including alcohol drinking and smoking history in this case? Considering the fact that he self-discharge from the hospital, etc., it is quite possible that his life has been disrupted, and this may have contributed to his lowered immunity. Please comment on this.

Reply: Thank you very much for your comments. The patient had a history of smoking and alcohol abuse. When the patient requested to be discharged, the chronic liver failure, spontaneous bacterial peritonitis (SBP), pulmonary infection, pleural effusion, and ascites were not cured. After the patient comprehensively considered his family's economic situation and his own condition, he discharged himself from the hospital against medical advice.

Comments 3: Related to #2, what was the cause of the liver cirrhosis in this case? Please show the results of virus and autoimmune markers.

Reply: Thank you very much for your comments. The patient was not treated with artificial liver. Considering the medical expenses and prognosis, the patient and their family members refused the artificial liver treatment. He was treated with magnesium isoglycyrrhizinate for hepatoprotective therapy. The patient had a history of alcohol abuse.

HBsAb, 29.19 mIU/mL, HBcAg, 8.88 S/CO; hepatitis E antibody IgG, weakly positive, cytomegalovirus antibody IgG, positive; coxsackie virus antibody IgG, positive (Line 28, Page 6- Line 12, Page 7).

Alcohol and some of the above viruses may be factors that cause liver failure.

Comments 4: Please illustrate and explain the figure more clearly by using arrows.

Reply: Thank you very much for your comments. It has been modified according to the comments of the reviewer (**Figure 2 to Figure 5**).

Reviewer #3:

Scientific Quality: Grade C (Good)

Language Quality: Grade B (Minor language polishing)

Conclusion: Minor revision

Specific Comments to Authors: An extremely rare case report and you can perfectly detect the cause of bacteremia in these patients. Unfortunately, the patient refused medical treatment so that we cannot know the outcome of the patient.

Comments 1: The statement "HIV-negative" in the title has no meaning to this case report. Does the author have a specific reason to put that words in the title?

Reply: Thank you very much for your comments. Chiu et al.^[2] found that the incidence of MTB bacteremia in HIV-negative patients and HIV-positive patients were 0.024 and 6.2 per 1000 discharges, respectively ($p < 0.01$). There have been very few reports of HIV-negative cirrhosis patients with *M. tuberculosis* bacteremia.

Comments 2: Please provide specific data on the patient's physical examination! The patient had an abnormal liver function for two years without treatment, are there jaundice and signs of ascites? The patient has shortness of breath, how is the physical examination of the thorax area?

Reply: Thank you very much for your comments. It has been modified

according to the comments of the reviewer. (Line 13-19, Page 6) Physical examination of the skin showed the evidence of spider nevi, jaundice of skin or sclera, and facial features associated with liver disease, but no evidence of palmar erythema. Auscultation revealed abnormal breath sounds over both lungs and a decreased breath sounds over the right lower lung. Examination of the abdomen showed abdominal distension but no tenderness or rebound pain, splenomegaly, or percussion pain in the liver area. There were also no signs of asterixis.

Comments 3: Can the author determine whether the primary disease of *Mycobacterium tuberculosis* in this patient is an intrapulmonary or extrapulmonary case? Please give any specific reasons in the discussion section.

Reply: Thank you very much for your comments. It has been modified according to the comments of the reviewer. (Line 8-14, Page 10) We were unable to determine whether the primary disease of *M. tuberculosis* in this patient was an intrapulmonary or extrapulmonary infection because both ascites and blood cultures eventually showed growth of *M. tuberculosis* and *M. tuberculosis* can spread to different sites in the bloodstream.

Comments 4: The statement “the occurrence of *M. tuberculosis* bacteremia in cirrhotic patients has never been reported.” Is that true? On reference no. 10, there is 1 patient with the same condition as the author's patient. Please clarify!

Reply: Thank you very much for your comments. The sentence has been modified according to the comments of the reviewer (Lines 27-28, Page 9). The reference No. 10, there is 1 patient with the same condition as the patient.

Comments 5: Please CARE checklist guideline is filled by writing the page/line on each item.

Reply: Thank you very much for your comments. It has been modified according to the comments of the reviewer.

REFERENCES

1. **Rimola A**, García-Tsao G, Navasa M, Piddock LJ, Planas R, Bernard B, Inadomi JM. Diagnosis, treatment and prophylaxis of spontaneous bacterial peritonitis: a consensus document. International Ascites Club. *J Hepatol* 2000; [PMID: 10673079 DOI: 10.1016/s0168-8278(00)80201-9]
2. 10. **Chiu YS**, Wang JT, Chang SC, Tang JL, Ku SC, Hung CC, Hsueh PR, Chen YC. *Mycobacterium tuberculosis* bacteremia in HIV-negative patients. *Journal of the Formosan Medical Association* 2007; **106**: 355-364 [PMID: 17561470]