Author’s response to reviews

Title: Syphilitic hepatitis: A case report and review of the literature

Authors:

Jiaofeng Huang (huangjiaofeng@fjmu.edu.cn)
Su Lin (sumer5129@fjmu.edu.cn)
Mingfang Wang (wangmingfang@fjmu.edu.cn)
Bo Wan (wblu@163.com)
Yueyong Zhu (zhuyueyong@fjmu.edu.cn)

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Author’s response to reviews:

Dear Dr. Solera,

We would like to thank you and Dr. Barnes and Dr. Katzenstein for thoroughly reviewing our manuscript entitled ‘Syphilitic hepatitis: case report and review of the literature’ (BMGE-D-19-00220R1). We acknowledge the reviewers’ comments and constructive suggestions very much, which are valuable for improving the quality of our manuscript. We hope, with these modifications and improvements based on your suggestions and the reviewers’ comments, the quality of our manuscript would meet the publication standard of BMC Gastroenterology.

Sincerely,

Yueyong Zhu, M.D.
Associated Professor of Medicine
Liver Disease Research Center
The First Affiliated Hospital of Fujian Medical University
Email:zhuyueyong@fjmu.edu.cn

Here are our point-by-point responses:

To reviewer 1
Eleanor Barnes (Reviewer 1)

1. There is no sexual history given and no HIV test result-these are major omissions in the clinical
history and blood tests. If this history was not taken and the HIV test, not done—then this needs to be declared as a major omission in the case report.

Thank you for your suggestion. He denies the history of venereal exposure. Serological tests for HAV, HCV, HEV, HIV, EBV, and CMV were all negative. But we did not show it in the article. We have changed the sentence to “Biochemical examinations in our hospital revealed a weakly positive in hepatitis B surface antigen (HBsAg). His hepatitis B surface antibody, hepatitis B extracellular antigen (HBeAg) were both negative and his hepatitis B virus DNA was undetectable (&lt; 500 IU/ml). The other laboratory tests including Hepatitis A virus, Hepatitis C virus, Hepatitis E virus, human immunodeficiency virus, Epstein-Barr virus, cytomegalovirus, and other autoantibodies were all negative.” and marked with a red font.

2. The manuscript needs to be edited by an English speaker throughout as there are many grammatical and phrasing errors throughout.

Thank you for your careful work. We are so sorry for this mistake. Under your suggestion, we have already asked the native English speakers to help us re-read the manuscript and make the corresponding changes. Thank you.

3. More detail should be shown regarding the HBV serology (HBeAg, DNA, sAg), etc.

Thank you for your suggestion. Biochemical examinations in our hospital revealed a weakly positive in hepatitis B surface antigen (HBsAg). His hepatitis B surface antibody, hepatitis B extracellular antigen (HBeAg) were both negative and his hepatitis B virus DNA was undetectable (&lt; 500 IU/ml). We have marked with a red font.

4. Was HBV looked for in the liver biopsies? Was there evidence of liver fibrosis in the liver biopsy?

Thank you for your suggestion. Immunohistochemistry examination showed a weakly staining of HBsAg and HBeAg. He underwent liver biopsy and the results revealed granulomatous hepatitis with stage 2 inflammation and stage 1 fibrosis(Figure1C, D, E, and F). We have marked with a red font.

5. What are the main learning points from the case? The case could conclude with these?

Thank you for your suggestion. This case mainly tells us that unexplained intrahepatic cholestasis needs to consider the possibility of syphilitic hepatitis, and unexplained liver occupying also needs to consider syphilitic hepatitis. These views were also reflected in the discussion.

5. The authors state that the Mullick et al have defined the definition of syphilitic hepatitis—do the authors agree with this definition? What is the definition? This should be stated.

Thank you for these valuable comments. I agree with their point of view. The diagnosis of syphilitic hepatitis was made on the basis of the following criteria: (1) abnormal liver enzyme levels indicating hepatic involvement; (2) serological evidence for syphilis, with a positive RPR titer and a reactive FTA-Abs result or microhemagglutination assay result positive for T. pallidum (MHA-TP) in conjunction with an acute clinical presentation consistent with secondary syphilis; (3) exclusion of alternative causes of hepatic damage, such as acute viral hepatitis, use of medication, malignancy, or opportunistic infection; and (4) improvements in liver enzyme levels following appropriate antimicrobial therapy. These views were also reflected in the discussion.
6. Please state in the case report, what the Jarisch-Herxheimer reaction is-and how do you monitor for and identify this.

Thank you for these valuable comments. The Jarisch-Herxheimer reaction (JHR) is a transient immunological phenomenon seen commonly in patients during treatment for syphilis, and it manifests clinically with short-term constitutional symptoms such as fever, chills, headache, myalgias, even a sudden drop in body temperature and cold extremities may induce diffuse pulmonary bleeding besides exacerbation of existing cutaneous lesions. Sudden aggravation of the condition during treatment, you need to be alert to the possibility of JHR reaction, we can start by using small doses of antibiotics to prevent. Once the JHR occurs, experts noted a favorable response with prednisolone, especially in curtailing the febrile response in early syphilis.

To reviewer 2

Errese Lea Katzenstein (Reviewer 2) The authors describe a case of syphilitic hepatitis. The diagnosis was made by liver biopsy. Similar finding were reported recently (Murphy-CJ The Lancet Gasr & Hep 2017). However, the symptoms were clearly indicative of syphilis stage II. As far as I understand serological testing for syphilis was not done prior to the biopsy. Information about whether the cutaneous manifestation involved the soles and palms is lacking.

Minor points: The authors refer to their recent literature review - ref 1 - Journal name not included.

It is stated that the patient had hepatitis B - does this mean chronic hepatitis B?

1. However, the symptoms were clearly indicative of syphilis stage II. As far as I understand serological testing for syphilis was not done prior to the biopsy. Information about whether the cutaneous manifestation involved the soles and palms is lacking.

Thank you for these valuable comments. Yes, we did not have a syphilis check before the biopsy because it was not a routine test in our ward. Therefore, the diagnosis was delayed. The rashes were also observed on the soles and palms but not in this patient’s genitals. We have added this on the manuscript.

2. The authors refer to their recent literature review - ref 1 - Journal name not included.

Thank you for your careful work. We are so sorry for this mistake. We have changed the reference to “Huang J, Lin S, Wan B, Zhu Y. A Systematic Literature Review of Syphilitic Hepatitis in Adults. J Clin Transl Hepatol. 2018;6(3): 306-309.”

3. It is stated that the patient had hepatitis B - does this mean chronic hepatitis B?

Thank you for these valuable comments. Hepatitis B is the major differentiating diagnosis of this case. We ruled out chronic hepatitis B based on the following reasons.

1. Patients with hepatitis B usually have elevated ALT and AST rather than GGT and ALP.
2. This patient had lower HBsAg level (1.36 ng/ml, normal range 0-1 ng/ml) and negative HBeAg. The HBV DNA was undetectable. Liver biopsy revealed very slightly fibrosis, which ruled out a chronic liver injury. Altogether, this patient was less likely to be a chronic hepatitis B.