

Dear Editors and Reviewers:

We would like to express our sincere appreciation for your letter and for the reviewers' comments concerning our manuscript entitled "Be Aware of Abnormal Serum CA19-9 Levels: A Case Report of Splenic Retiform Haemangioendothelioma Concomitant with Haepatic Amyloidosis" (Manuscript NO.: 53323). Those comments are all valuable and very helpful for revising and improving our paper. The amendments made are marked in red in the revision paper and mentioned below:

Responds to the reviewer's comments:

Reviewer #1 (code: 03545890)

Response to comment: Interesting article. Congratulations for your well description.

Response: Thank you for your encouragement of the case report.

Reviewer #2 (code: 00722786)

1. Response to comment: What is the findings of the upper and lower endoscopy?

Response: We have added this part on page 8-9 according to the Reviewer's suggestion. Gastroscopy showed mild atrophic gastritis and mild intestinal metaplasia with dysplasia in gastric antrum. Sampled areas were Congo red stain- and methyl violet stain-negative. Colonoscopy showed mucosa chronic inflammation and mild dysplasia in focal glands with lymphoid tissue increasing in lamina propria. Sampled areas were Congo red stain- and methyl violet stain-negative. Evidence of amyloid deposits was not found based on above histological findings.

Response to comment: What is the serological status for other hepatotropic viruses (except HBV)?

Response: We are very sorry for our negligence of writing serological status of hepatotropic viruses (except HBV) and non-hepatotropic viruses as we thought the result was not significant. Both of them were negative. We have added serologic investigation of viruses on page 7.

Response to comment: Literature data suggest that elevation of CA-19-9 may be caused by amyloidosis, and further explanation is needed.

Response: It is really true as reviewer suggested that we should further explain the relationship between CA19-9 and amyloidosis. Amyloid deposits would compress bile ductules in hepatic amyloidosis. Several researches observed an obvious correlation between CA19-9 and cholestasis. CA19-9 is secreted in a mucin bound form by the biliary and gallbladder mucosa and is exclusively excreted in bile. In the cholestatic situation, overload bile leads CA 19-9 epitope to release to the blood circulation.

Besides, the liver size was larger increasingly and it is consistent with CA 19-9 before surgical excision of the spleen. During follow-up, CA 19-9 level decreased but it did not reach the normal range after surgery. Therefore, we speculated that a potent mechanism of hepatic amyloidosis may be related with CA 19-9. We have added this part on page 11.

4. Response to comment: Secondary amyloidosis may be due to chronic infection, if it is ruled out in this case?

Response: As Reviewer considered that chronic infection could lead to secondary amyloidosis. However, firstly the patient did not present any clinical manifestation of chronic infection such as fever, local swelling, pain, vomiting and so on. Secondly, markers of inflammatory response including leukocyte count, lymphocyte count, C-reactive protein, autoimmune rheumatic indicators were normal. Lastly, infection of bacteria or

virus (except HBV) was ruled out through serologic investigation and biopsy. The patient had history of carrying inactive HBsAg but HBV DNA were negative. Therefore, we thought chronic infection is a little less likely to result in secondary amyloidosis in this case. We have added this part on page 7 and page 11.

Besides, according to the Guidelines and Requirements for Manuscript Revision, we added timeline on page 6 and Personal and family history on page 7.

We tried our best to address all issues raised by reviewers which we hope meet with approval. We appreciate for editors and reviewers' warm work earnestly and we are glad to respond any further questions and comments that you may have. Once again, thank you very much for your comments and suggestions.

Yours sincerely,

Sun KD