April 25, 2013

Dear Editor,

Please find enclosed the edited manuscript in Word format.

**Title: Epstein-Barr virus negative primary hepatic leiomyoma: case report and review**

**Author: Xianzhang Luo, Changsheng Ming , Xiaoping Chen, Nianqiao Gong**

**Name of Journal:** *World Journal of Gastroenterology*

**ESPS Manuscript NO:** 2886

The manuscript has been improved according to the suggestions of reviewers:
1 Format has been updated

2 Revision has been made according to the suggestions of the reviewer

## Reviewer 1 (01553776)

Major points: This case report is very briefly written. In fact, the patient had been on immunosuppressive regimens (not regimes) of tacrolimus, azathioprine and prednisolone. It was not clarified how long and how much doses the patient was on such a therapy. More detailed information is required.

Response: We agree the reviewer's opinion fully. To describe a clinical event of the patient who is on immunosuppressive regimens, it is necessary to show the related details. In the revised manuscript, we give the detailed information of the immunosuppressive agents, including the level of tacrolimus and the dose of azathioprine and prednisolone. Meanwhile, the regimes is corrected as regimens. We thank the author very much for this comment, which improves our manuscript.

Also, the patient's immunological profiles such as absolute lymphocyte counts, data on flowcytometric T-cell, B-cell analysis as well as T-cell function are required. The authors did not mention if the patient was actually immune-compromised or if the development of hepatic leiomyoma was related to current or previous immunosuppressive treatment.

Response: The reviewer gives us a very important comment and it is absolutely helpful for the quality improvement. We thank the author very much! In the revised version, we add some data of lymphocytes. The patient is an allograft recipient on immunosuppressive regimens for 9 years, therefore he is definitely under the immune-compromised status. However, to date the knowledge about the relationship between T-cell function and tumor development is not clear enough because the development of tumor has too complicated mechanisms. As we have discussed in our manuscript, in the 28 reported primary hepatic leiomyoma patients, only **25**% (7/28) were immunocompromised (6 transplanted and 1 HIV). On the other hand, in all the reported cases (5 cases) who were examined EBV infection, **100**% (5/5) exhibited positive result, indicating a very strong relationship between the EBV infection and the development of primary hepatic leiomyoma. Based on the knowledge, we don't think

the T-cell function assay (e.g. MLR, ATP-assay by immuno-cylex) is real helpful to explain the tumor development. Very interestingly, our case is EBV negative, different from all the other reported cases, indicating that EBV infection is important but neither necessary nor sufficient for the development of primary liver leiomyoma. This observation highlights the complex and heterogeneous nature of the disease and raises the question whether EBV is a passenger rather than a causative agent for this tumor.

EBV-negativity was discussed only by EBER-ISH results; but readers may want to know EBV genome copies in peripheral blood as well as serum anti-EBV-titers.

Response: The data of EBV are very important. The EBV infection in this case was negative: including the serological testing and EBER-ISH, which was described in the manuscript.

Table 1 includes 4 pediatric (age <18 years) cases. Comments are required if the developmental mechanism(s) are the same or different between pediatric and adult cases. This case is better included in the Table as Present case for comparison of the data with those of the published cases.

Response: We thank the reviewer for this comment. The developmental mechanisms between the pediatric and the adult will form a very interesting area. We would to push this study in the future. Therefore, we include a related comment in our manuscript. This modification will deepen our knowledge on primary hepatic leiomyoma.

Minor points: (1) The authors claim that this is the 29th case in the world; but readers may doubt how accurate and thorough the authors' survey was. Maybe, it is better say that the authors found at least 28 cases in the literature.

Response: We thank the reviewer for this comment. We modified the sentence as "only 28 reported cases have been identified in the literature in the 86-year history worldwide". With this modification, the manuscript becomes more accurate.

(2) In Introduction, only 27 cases, and In Discussion, only 28 cases.

Response: Thank the reviewer very much! We have already corrected the error.

(3) Page4, line 6; DOG1 (Discovered on GIST1) is better.

Response: Thanks a lot! We have followed this comment.

(4) Figure BCD were all HE staining; why not showing specific alpha-SMA or desmin

Response: We agree this comment. In the revised version, B: the tumor (arrow) and the normal liver tissue, HE staining ×200; C: α-SMA staining (arrow) of the tumor tissues, immunohistochemical staining×200; D: desmin staining (arrow) of the tumor tissues, immunohistochemical staining×200. The current Fig 2 therefore provides more information to the reader with an improved quality. We thank the reviewer again.

(5) Figure 3; because the results were negative, maybe positive and negative controls are better to be shown together.

Response: We agree this comment. In the revised version, we have given the positive control.

**Reviewer 2 (00483991)**

An interesting case report showing EBV infection is neither necessary nor sufficient for the development of primary liver leiomyoma. This observation highlights the complex and heterogeneous nature of the disease and raises the question whether EBV is a passenger rather than a causative agent for this malignancy. It is clear more research is needed in understanding the mechanism behind this rare but interesting cancer. Of note, table 1 is an excellent resource. Well done.

Response: Thank you very much for your support.

Comments - References needed in the introduction. –

Response: We agree the reviewer's opinion. The related references have been given in the introduction.

In the discussion I would recommend the authors discuss the requirement of an international primary hepatic leiomyoma sample bank to allow researchers to untangle its complex pathogenesis using current omics- and system-based methodologies.

Response: We agree the reviewer's opinion. We give this suggestion in the revised version. I am sure this suggestion is benefit to push the investigation on the underlying mechanisms of primary hepatic leiomyoma. We thank the reviewer very much!

3 References and typesetting were corrected

Thank you again for publishing our manuscript in the *World Journal of Gastroenterology*.

Sincerely yours,
Dr. Nianqiao Gong