

April 30, 2015

Dear Editors at World Journal of Gastroenterology,

Please find enclosed edited manuscript in Word format (file name: WJG_Review_AsanoN_R1_submission.docx) and the figure in Powerpoint format (file name: WJG_Review_figure.pptx).

Title: *Helicobacter pylori*-negative gastric MALT lymphomas

Authors: Naoki Asano, Katsunori Iijima, Tomoyuki Koike, Akira Imatani, Tooru Shimosegawa

Name of Journal: World Journal of Gastroenterology

ESPS Manuscript no.: 17677

The manuscript has been improved according to the suggestions of the reviewers. The changes are highlighted in the manuscript.

1. Format has been updated.
2. We had this manuscript checked by a professional English editing company. The certificate is attached below.
3. We added a description about the drug resistance in Treatment section.
4. We have now added another Table, which shows the main differences between *H. pylori* positive and negative MALT lymphomas.
5. We removed the last sentence in the Conclusion section.
6. We added Figure 1, which is a scheme of API2-MALT1 induced NF- κ B activation.
7. We have corrected *Chlamydia psittaci* to its newer name *Chlamydophila psittaci*.
8. We added the possible involvement of autoimmune diseases in Pathogenesis section.
9. We added a description about the non-specific symptoms of gastric MALT lymphoma patients in the Diagnosis section.
10. We added the explanation for the combined *H. pylori* detection method in the Diagnosis section.

11. We added a description about the increasing drug resistance of *H. pylori* in the Treatment section.

12. References were corrected.

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

Sincerely yours,

Naoki Asano

Division of Gastroenterology, Tohoku University Graduate School of Medicine

Point-by-point reply to reviewers' comments

Reviewer 1:

The whole paper need to a English error-checking.

The authors appreciate the reviewer's comment. We had this manuscript checked by a professional English editing company.

Reviewer 2:

This manuscript showed the detail of those H. pylori-negative gastric MALT lymphomas to us. The contents were comprehensive for the readers. It is worth for recommendation. However, there are some minor problems in it as following:

1. The eradication of H. pylori becomes more difficult due to many factors (such as drug resistance). So the traditional triple therapies meet the challenge and many alternative first-line and rescue therapies are presented. I think that the authors should mention this point in the part of Treatment.

The authors appreciate the reviewer's comments. We added a description about the drug resistance in Treatment section.

2. In order to make readers easily understanding the difference between H. pylori positive and -negative MALT lymphomas, the authors should make t table to list the main difference.

The authors appreciate the reviewer's comments. We have now added another Table, which shows the main differences between H. pylori positive and negative MALT lymphomas.

Reviewer 3:

The authors are presenting a comprehensive review of an

important topic. This is a well-written manuscript with adequate number of recent references. No major comments. The minor recommendations for improvement include some language polishing by a native English speaker both in abstract and main text. Major attention has to be paid to the following sections: Introduction, Pathogenesis, Diagnosis, Conclusions (e.g. the last sentence has to be either withdrawn or formulated according to the message in Conclusions)

The authors appreciate the reviewer's comments. We had this paper checked by a professional English editing company. We agree that the last sentence is unnecessary and it is now removed in this revision.

Reviewer 4:

The manuscript entitled: " Helicobacter pylori-negative gastric MALT lymphomas" presents very interesting problem of pathogenesis, diagnosis and treatment of MALT lymphomas caused by other factors than H. pylori infection. The work represents review papers. The work is properly constructed and well written. However, following modifications are needed for its acceptance: Abstract: The authors presents the study aims and the rationale of the study are well specified. In the section: Pathogenesis: The authors stated that "chronic infection with H. pylori is considered to attract lymphoid cells to the gastric MALT:. It is true of course, but it would be better to specify the exact mechanism of this pathogenesis and the role of CagA and cytotoxin VacA in carcinogenesis. The association of gastric MALT lymphoma with dysregulation of the NFkappaB pathway is well clarified in the study however it would be better to present it on the image or schedule. Some additional, more detailed information should be added about other microorganisms

involved in pathogenesis of MALT lymphomas, especially *H. heilmannii*. It should be stated *Chlamydophila psittaci*, not *Chlamydia psittaci* (former name). It would be good to emphasize that besides infectious etiology, some autoimmune diseases, such as Sjögren syndrome or Hashimoto thyroiditis, can also be associated with development of MALT lymphomas. In the section: *Diagnosis* The endoscopic findings should be presented more clearly with a more accurate description, characteristics and localization of changes in the stomach. It should be stated that the typical symptoms in the case of MALT lymphomas are usually vague, and the lesions are usually nonspecific. It should be also emphasized that the diagnosis of *H. pylori* infection should be always performed and excluded. The authors stated that: "It is always important to combine different methods such as urea breath test, endoscopy, histopathology, serology, stool antigen tests etc., together to exclude the possibility of false-negative result. This statement should be clarified, what kind of methods? All of them? Generally, a non-invasive method should be combined with an invasive one ex. urea breath test, or stool antigen tests with histopathology. In the section: *Treatment* The authors stated that: The standard antibiotic therapy consists of combination of amoxicillin, clarithromycin and PPI. This statement should be clarified, because in the standard antibiotic therapy metronidazole can be used also as a first line treatment, especially in countries where the resistance of *H. pylori* strains to clarithromycin is high. The table shows previous reports on the presented subject. References: not fully updated, more than 50 % of the references are older than 6 years, moreover in my opinion there are too many references in the manuscript. It would be better if the authors select them more precisely. Presentation: The manuscript requires some formal revision.

The authors appreciate reviewer's comments.

We now added Figure 1, which is a scheme of API2-MALT1 induced NF- κ B activation.

We have corrected *Chlamydia psittaci* to its newer name *Chlamydophila psittaci*.

We added the possible involvement of autoimmune diseases in Pathogenesis section.

We added a description about the non-specific symptoms of gastric MALT lymphoma patients in the Diagnosis section.

We added the explanation for the combined *H. pylori* detection method in the Diagnosis section.

We added a description about the increasing drug resistance of *H. pylori* in the Treatment section.

We corrected the references.

The authors thank the reviewers for taking their time and reviewing our manuscript. We really appreciate your help in improving our manuscript.