Name of journal: World Journal of Gastroenterology
Manuscript NO: 56953

Dear Editor,

Dear reviewers,

Thank you for your time to revise our Manuscript ID: 56953, Surveillance of Russell Body Helicobacter Pylori-negative gastritis: case report and literature review.
Authors: Milena Peruhova, Monika Peshevska-Sekulovska, Viktoriya Georgieva, Gabriela Panayotova, Dorian Dikov.
We have incorporated most of the suggestions made by the reviewers. Those changes are highlighted within the manuscript. Please see below, in blue, for a point-by-point response to the reviewers' comments. All page numbers refer to the revised manuscript file with tracked changes.

Reviewer #1 No. 03478404

The manuscript titled "Surveillance of Russell Body Helicobacter Pylori-negative gastritis: case report and literature review" is written in an elegant manner, clear, generally with attention to details and easily to be followed. Data presented are of high scientific quality. The structure is respected and all paragraphs include appropriate info. Especially the Discussion paragraph is very well written and explained, with reference to the data from literature. Every case was thoroughly analysed. The quality of figures regarding the diagnosis of RBG is very good and the figures definitely support the diagnosis. CARE Checklist–2016 is correct. The manuscript deserves to be published. Comments/questions/suggestions: A. Title – well-chosen and illustrative, but contains more than 12 words. B. Abstract: 1. The authors wrote: "patient underwent endoscopic surveillance"; that would mean that he had a previous endoscopy. This does not appear from the main text. Therefore, probably it should be written "underwent both upper and lower endoscopy, as part of investigations for his mild iron deficiency anemia". This should also be corrected in the main text. 2. I wonder – Hemoccult test was performed before endoscopies? Was it positive? It does not appear in the main text either. 3. Figure 1 in the main text also shows nodularity. This lesion is neither mentioned in the Abstract, nor in the main text. 4. Why did the authors consider "preliminary diagnosis - diffuse type of gastric carcinoma" and

not also other tumours (lymphoma, plasmocytoma)? Same question for the main text. 5. Why did the authors choose to administer PPI? 6. Did anemia disappear after therapy? I did not find this in the main text. This is very important. Was RBG the cause of anemia? Or RBG was diagnosed by chance, performing upper endoscopy, since no GI symptoms were present? The authors mentioned that the endoscopy did not improve, only histology. C. Core Tip: 1. The authors wrote "Endoscopic findings include vast spectrum of nonspecific features"; however, in the Abstract only hyperemia and edema are mentioned. 2. The patient had an 8-week period of therapy with PPI. Why do the authors consider this a long time period, responsible for the "complete extinction of RB and Mott cells over time" - that would mean after 12 months… D. Introduction: 1. Please write "Russell body gastritis", before the first abbreviation (first line)? 2. Please insert what Databases were searched and the time period (cases in the literature). E. CASE. 1. Laboratory examinations: the level of ferritin is not mentioned, neither the Hemoccult test nor the inflammatory serological markers. Serum iron on the lower reference limit - that means the level was still normal and there was only slightly elevated value of total iron binding capacity. Why then iron-deficiency anemia? Please report on ferritin level and on inflammatory serological markers. 2. Did the authors proceed to an invasive method (upper and lower endoscopy) before these tests? 3. Case presentation should not contain data from literature. I suggest the sentence "According to the literature, mucosal infiltration with RB and Mott cells may be associated with infectious or autoimmune processes [10,14,16-18]." to be used in "Discussion". And write directly "We ruled out…". 4. I also suggest to write directly that "we did not check for M protein in the serum, we did not perform Bence-Jones protein urine test, TB-spot, EBER in situ hybridization or trephine biopsy of the bone marrow.". Limitations of the diagnostic algorithm should be described in "Discussion". 5. What is not mentioned: did anemia disappear or not? G. Conclusion: concise and clear. 1. Could the authors propose any protocol for the follow-up endoscopies (schedule)? 2. Could they propose some non-invasive markers to be studied in the future, which would avoid endoscopies? E. Figures: Figure 4 – please insert after "Distribution of RBs in the stomach": in all cases from the literature. Figure 5: Please insert after "Associated conditions in patients with H. pylori-negative RBG", according to the available literature. F. Table 1 is of good quality and clear. I would suggest, since all cases are H. Pylori negative (and it is understandable from the title of the Table), that the column regarding presence of H. Pylori be removed. H. References [10, 14, 16, 18] were used before references 8, 9, 11-13, 15 and 17. The references in Discussion are not in order; please revise. Otherwise, references are pertinent and up-to-date. I. Conflict-of-Interest Disclosure Form should be reviewed.

A. Title – well-chosen and illustrative, but contains more than 12 words.

- Thank you for pointing out the mistake in our title. We changed the title: "Surveilling Russell Body Helicobacter Pylori-negative gastritis: case report and literature review.

B. Abstract: 1. The authors wrote: "patient underwent endoscopic surveillance"; that would mean that he had a previous endoscopy. This does not appear from the main text. Therefore, probably it should be written "underwent both upper and lower endoscopy, as part of investigations for his mild iron deficiency anemia". This should also be corrected in the main text.

- We are grateful for the important note. We acknowledge for not being absolutely correct when using the term "surveillance". So, we have changed the term "surveillance" in the text as "screening".

2. I wonder – Hemoccult test was performed before endoscopies? Was it positive? It does not appear in the main text either.

- We appreciate insightful comment. However, our patient did not perform Hemoccult test before endoscopy. According to our National society protocol patients above 50 years of age with iron-deficiency anemia of unknown etiology should undergone endoscopic screening.

3. Figure 1 in the main text also shows nodularity. This lesion is neither mentioned in the Abstract, nor in the main text.

- Thank you for the valuable remark. We acknowledge for not being absolutely correct with our description of endoscopic image. We have added "nodularity "in the abstract and in the main text.

4. Why did the authors consider "preliminary diagnosis - diffuse type of gastric carcinoma" and not also other tumours (lymphoma, plasmocytoma)? Same question for the main text.

- We think this is an excellent remark. Our preliminary diagnosis was diffuse type of gastric carcinoma, based on endoscopic findings: well demarcated line between the corpus and the antrum of stomach as well as the proximal localization of mucosal abnormalities. According to your recommendation, we have added lymphoma and plasmocytoma to the differential diagnosis in the abstract and in the main text.

5. Why did the authors choose to administer PPI?

- We chose this treatment strategy, based on histology results: H. Pylori-negative Russell body gastritis. We excluded the most common conditions which lead to accumulation of Mott cells in gastric mucosa. To the best of our knowledge there were no treatment

recommendations published in the literature so far. Thus, we decided to treat our patient with PPI for a longer period of time.

6. Did anemia disappear after therapy? I did not find this in the main text. This is very important. Was RBG the cause of anemia? Or RBG was diagnosed by chance, performing upper endoscopy, since no GI symptoms were present? The authors mentioned that the endoscopy did not improve, only histology.

- We administered intravenous iron medication after first endoscopy. As mentioned in the main text three months' later patient came for follow-up and his blood tests showed slight increase of his Hb level (117 g/L). RBG was diagnosed by chance. Whether RBG is the cause of anemia or an early symptom of another disease is uncertain. For this reason, this patient should undergo regular follow-up.

C. Core Tip: 1. The authors wrote "Endoscopic findings include vast spectrum of nonspecific features"; however, in the Abstract only hyperemia and edema are mentioned.

- Thank you for pointing this out. We corrected the endoscopic description of the gastric mucosa in the abstract as well as in the main text, as you recommend. You can follow-up the changes via track changes.

2. The patient had an 8-week period of therapy with PPI. Why do the authors consider this a long time period, responsible for the "complete extinction of RB and Mott cells over time" - that would mean after 12 months…

- We consider PPI therapy for H. Pylori-negative RBG based on the theory that Mott cell are most commonly associated with chronic inflammation. Since the integrity of gastric mucosa is not preserved, the secretion of hydrochloric acid may lead to additional damage. With the use of PPI, on the one hand we intended to reduce the chronic inflammation, and on the other hand to preserve the mucosa from the aggressive factors.

D. Introduction: 1. Please write "Russell body gastritis", before the first abbreviation (first line).

- We have corrected that in the Introduction as you recommended.

2. Please insert what Databases were searched and the time period (cases in the literature).

- We searched the electronic databases for scientific literature PubMed and Google Schooler and identified 41 scientific publications that use the keywords: Russell body

gastritis; H. pylori-negative; Treatment; Mott cells. A total of 41 publications were published during the period 1998-2020 are included.

E. CASE. 1. Laboratory examinations: the level of ferritin is not mentioned, neither the Hemoccult test nor the inflammatory serological markers. Serum iron on the lower reference limit - that means the level was still normal and there was only slightly elevated value of total iron binding capacity. Why then iron-deficiency anemia? Please report on ferritin level and on inflammatory serological markers.

- Thank you for your constructive comment. As we pointed out above, we did not perform Hemoccult test of the patient. We added levels of ferritin, total iron binding capacity and inflammatory serological markers in the main text. The value of ferritin was 18.43ng/ml (30-400ng/ml), value of total iron binding capacity was 83.2µmol/L (45-72µmol/L) and the value of CRP was 0.30ml/L (0-5mg/L). Based on those biochemistry results, we came to conclusion mild iron-deficiency anemia.

2. Did the authors proceed to an invasive method (upper and lower endoscopy) before these tests?

- We did not perform upper and lower endoscopy before the blood tests.

3. Case presentation should not contain data from literature. I suggest the sentence "According to the literature, mucosal infiltration with RB and Mott cells may be associated with infectious or autoimmune processes [10,14,16-18]." to be used in "Discussion". And write directly "We ruled out…".

- Thank you for the valuable remark. We took into account your comment and we made the changes in "Discussion" as you recommend.

4. I also suggest to write directly that "we did not check for M protein in the serum, we did not perform Bence-Jones protein urine test, TB-spot, EBER in situ hybridization or trephine biopsy of the bone marrow.". Limitations of the diagnostic algorithm should be described in "Discussion".

- We have corrected the passages in the main text regarding this issue. You can follow-up the changes via track changes.

5. What is not mentioned: did anemia disappear or not?

- ✓ As we mentioned in the text when the patient came for follow-up, his blood tests showed slight increase of his Hb level (117 g/L). Anemia did not disappear.

G. Conclusion: concise and clear. 1. Could the authors propose any protocol for the follow-up endoscopies (schedule)?

- ➢ Thank you for your valuable note about the conclusion part of the manuscript. At this moment we cannot recommend endoscopic protocol for follow- up because of the insufficient studies published so far.

2. Could they propose some non-invasive markers to be studied in the future, which would avoid endoscopies?

- ➢ More data and more research have to be conducted in order to propose diagnostic non-invasive markers about this rare entity.

E. Figures: Figure 4 – please insert after "Distribution of RBs in the stomach": in all cases from the literature. Figure 5: Please insert after "Associated conditions in patients with H. pylori-negative RBG", according to the available literature.

- ➢ Thank you for pointing this out. We have changed your remarks in Figure 4 and Figure 5.

F. Table 1 is of good quality and clear. I would suggest, since all cases are H. Pylori negative (and it is understandable from the title of the Table), that the column regarding presence of H. Pylori be removed.

- ➢ Thanks for your remark. We have changed the table as you recommend.

H. References [10, 14, 16, 18] were used before references 8, 9, 11-13, 15 and 17. The references in Discussion are not in order; please revise. Otherwise, references are pertinent and up-to-date.

- ➢ Thank you for your remark about the reference order. We have corrected them in an appropriate way.

I. Conflict-of-Interest Disclosure Form should be reviewed.

Reviewer #2 No. 02510721

The manuscript is very interesting. The Authors show a rare case report and develop a correct and complete analysis of the etiology, pathogenesis and clinical characteristics of Russell body gastritis. The Case report is well performed. The Discussion evaluates in particular the clinical problems of the H. pylori-negative RBG versus the cases with H. pylori infection. Also appropriate the review of the literature. The Conclusion synthetizes the various clinical and therapeutic features of the pathological condition. Correct and useful the Figures and Table. The References are up-to-date.

- We are grateful for your positive evaluation of the manuscript.

Reviewer #3 No. 00722050

Russell body gastritis (RBG) is a rare form of chronic gastritis which mostly affects the antrum and has a male predominance. The diagnosis relies on histology and immunohistochemistry (IHC). It is characterized by accumulation of plasma cells containing RB and Mott cells in gastric mucosa and appropriate IHC staining. The data presented are convincing and this 51-years-old patient has indeed RBG. The manuscript is well written. My only suggestion is that the authors should point out in the discussion that a lymphoma (before histology and IHC) was in the differential. Thus, flow cytometry of a biopsy would be important for future cases.

- Your evaluation of the manuscript is of a great importance to us. Thus, we are grateful for your time and overall positive assessment of the manuscript. Thank you for pointing this out. We agree this is an important consideration. We have already mentioned that in the Discussion. However, we included your suggestion in the case presentation.

Reviewer #4 No. 03026651

Thank you for this interesting paper. However, few points are better to be cleared: 1. When you say surveillance gastroscopy for the first endoscopy, did he undergo previous gastroscopy? (before the index one) 2. Did you do duodenal, ileal and colonic biopsies? 3. Did you consider

H. Pylori eradication despite negative biopsies? did you consider any other tests for H. Pylori detection? Regards

When you say surveillance gastroscopy for the first endoscopy, did he undergo previous gastroscopy? (before the index one)

- The notes from the reviewers are addressed above in the comment of Reviewer #1 No. 03478404

Did you do duodenal, ileal and colonic biopsies?

- We did not obtain duodenal, ileal and colonic biopsies, as there were no endoscopic abnormalities of the mucosa. We have added this information to our case report. You can follow-up the changes via track changes.

Did you consider H. Pylori eradication despite negative biopsies? Did you consider any other tests for H. Pylori detection?

- Thank you for the valuable remark. The patient performed fecal test for H. pylori in outpatient settings before the first admission, which was negative. Moreover, there was reduction in Russell bodies after the treatment with PPI. Therefore, we did not consider performing any additional H. Pylori tests, as well as H. Pylori eradication.

1.Science Editor: 1 Scientific quality: The manuscript describes a case report of the Helicobacter pylori-negative gastritis. The topic is within the scope of the WJG. (1) Classification: Grade B, Grade B, Grade B and Grade C; (2) Summary of the Peer-Review Report: Russell body gastritis is a rare form of chronic gastritis which mostly affects the antrum and has a male predominance. The Authors show a rare case report and develop a correct and complete analysis of the etiology, pathogenesis and clinical characteristics of Russell body gastritis. However, there are some issues should be addressed. The authors need to add more details in the “case presentation” section. The authors should point out in the discussion that a lymphoma (before histology and IHC) was in the differential. The questions raised by the reviewers should be answered; and (3) Format: There is 1 table and 5 figures. A total of 28 references are cited, including 3 references published in the last 3 years. There are no self-citations. 2 Language evaluation: Classification: Grade A, Grade B, Grade B and Grade B. 3 Academic norms and rules: The authors provided the signed Conflict-of-Interest Disclosure Form and Copyright License Agreement, and the Written informed consent. No academic misconduct was found in the CrossCheck detection and Bing search. 4 Supplementary comments: This is an unsolicited manuscript. The study is without financial support.

The topic has not previously been published in the WJG. The corresponding author has not published articles in the BPG. 5 Issues raised: Please provide the original figure documents. Please prepare and arrange the figures using PowerPoint to ensure that all graphs or arrows or text portions can be reprocessed by the editor. 6 Re-Review: Required. 7 Recommendation: Conditionally accepted.

- ✓ Thank you for your time and overall positive evaluation of the manuscript. The notes from the reviewers are addressed above. We will prepare and arrange all the figures as you recommended.
- ✓ We have one self-citation of our papers related to the subject:

15. Bozhkova DM, Dikov D. Should we perform cytokeratin immunostaining in cases of Russell body gastritis? Ann Diagn Pathol 2020; 46: 151524 [PMID: 32302922 DOI: 10.1016/j.anndiagpath.2020.151524]

(2) Editorial Office Director: I have checked the comments written by the science editor.

(3) Company Editor-in-Chief: I have reviewed the Peer-Review Report, full text of the manuscript, and the relevant ethics documents, all of which have met the basic publishing requirements of the World Journal of Gastroenterology, and the manuscript is conditionally accepted. I have sent the manuscript to the author(s) for its revision according to the Peer-Review Report, Editorial Office's comments and the Criteria for Manuscript Revision by Authors.

- ✓ Thank you for your time and overall positive evaluation of the manuscript. All comments, remarks and notes from the reviewers are addressed above.
- ✓ The revised version of the manuscript is provided as editable Word format where all changes during revision could be followed-up.