Tuesday, 21st June 2023

Dear Editors,

Please find enclosed the revised manuscript "*INCIDENCE AND PREVALENCE OF GASTRIC NEUROENDOCRINE TUMORS IN PATIENTS WITH CHRONIC ATROPHIC AUTOIMMUNE GASTRITIS",* which we are re-submitting for your consideration.

We have performed the revision as per the suggestions of the reviewers, and we hope that the manuscript will now be suitable for publication in *World Journal of Gastrointestinal Oncology.*

The authors wish to thank the Editor and the Reviewers for their insightful comments which have helped to improve the work's quality. The authors are humbled that you have pointed out the strengths and weaknesses of the manuscript.

Please find below a point-by-point response to the comments.

All changes have been highlighted in the text, as requested in the instructions for authors.

Reviewer #1:

Scientific Quality: Grade B (Very good)

Language Quality: Grade B (Minor language polishing)

Conclusion: Accept (High priority)

Specific Comments to Authors: In this study, authors assessed the incidence and prevalence of type I gNENs in a cohort of AIG patients as well as circulating levels of chromogranin A (CgA) and gastrin. They confirmed that type I gNENs represent a non-negligible complication in patients with AIG and that they are related to hypergastrinemia. On the other hand, they found that the serum gastrin level cannot be identified as a noninvasive marker of early diagnosis of gNEN in AIG because of its low specificity. The results are clearly presented, and the conclusions are hardly controversial. It is scientifically sound and contains sufficient interest and originality to merit publication.

We sincerely thank the reviewer for the positive comments, which summarized well the limitations and strengths of the study. The ultimate goal of this study is to assess the occurrence of gNENs in AIG analyzing, among variables commonly considered in clinical practice, whether there are noninvasive markers of neuroendocrine tumors in the population of patients with AIG to ensure their earliest possible diagnosis. Despite the hardly controversial results, we claim to have contributed to a little more clarity in this field, for which many scientific efforts are still needed to date.

Reviewer #2:

Scientific Quality: Grade C (Good)

Language Quality: Grade B (Minor language polishing)

Conclusion: Major revision

Specific Comments to Authors: The paper did not analyze some factors related to autoimmunity, only listed them in case screening. We do not know the impact of autoimmunity on the GASTRIC NEUROENDOCRINE

TUMORS. The purpose of analyzing cause did not achieved, which cannot bring much help to prevention and treatment.

We thank the reviewer for the clarification and apologize for not presenting the results clearly enough. As mentioned in the Materials and Methods" section, the following concomitant autoimmune diseases were recorded for each included patient: Thyroiditis, celiac disease, type 1 diabetes mellitus, vitiligo, psoriasis, Addison's disease, myasthenia, fibromyalgia, oral lichen planus, autoimmune liver disease, autoimmune connective tissue disease, and autoimmune polyglandular syndrome. At baseline, 72% of patients had at least one autoimmune endocrine disease, with autoimmune thyroid disease being the most common (35.8%). When distinguishing between AIG patients who had developed one or more neuroendocrine tumors and AIG patients who had not, no statistically significant differences were found in the baseline prevalence of the listed concomitant immune-mediated diseases. For completeness, the authors have added this finding to both the manuscript text (see Results section, page 11) and the accompanying Table 2 (see page 18).

Reviewer #3:

Scientific Quality: Grade C (Good)

Language Quality: Grade A (Priority publishing)

Conclusion: Minor revision

Specific Comments to Authors: The authors presented an interesting manuscript on neuroendocrine tumors of stomach carcinogenesis in patients with autoimmune atrophic gastritis. The article is well illustrated. The manuscript does not correspond to the review. It follows the format of an observational study. The authors are invited to read and analyze in the introduction the articles by Professor Helander HF on the topic of the manuscript. Please add these links to the reference. I propose the authors to discuss two hypotheses of the transformation of neuroendocrine gastric cells in the manuscript. 1. Functional physiological hypertrophy of neuroendocrine cells (ECL) as a result of hypergastrinemia as a result of autoimmune atrophic gastritis and long-term use of proton pump inhibitors (PPIs). 2. Pathological hyperplasia of neuroendocrine cells - carcinogenesis of the stomach. This scientific topic needs to be continued of clinical assay. The manuscript is recommended for publication in the World Journal of Gastroenterology after revision.

We thank the reviewer once again for their suggestions, which helped to improve the quality

As correctly noted, this is an observational study, so the authors have changed the title of the front page (see page 1). The authors apologize for the inaccuracy.

We thank the reviewer for the bibliographic reference to the in vivo animal studies by Prof. Helander, which present mainly histological results in support of the trophic role of gastrin on gastric mucosa. In particular, a very interesting article (PMID 8565765) has highlighted the fact that administration of 60 nmol/kg/day gastrin-17 or of 400 mumol/kg/day omeprazole in rats undergoing gastric ulcer induction resulted in a significant increase in the epithelial labeling index of the ulcer compared with controls, demonstrating the trophic role of gastrin on gastric mucosal proliferation/regeneration. Reference to this article was added in the manuscript (ref 10, see pages 4 and 13).

Although it is true that chronic therapy with PPI leads to an increase in circulating gastrin levels and may therefore contribute to gastric mucosal hypertrophy, PPI are not yet clearly considered carcinogens. In

any case, the potential bias associated with chronic PPI use was removed from the study population because all patients considered had to meet the criterion of at least 15 days of suspension to be included in the study (see Materials and Methods chapter – Endoscopic Studies section).

In conclusion, the authors thank the reviewer for the interesting insight into the distinction between simple hyperplasia of the gastric mucosa as a consequence of hypergastrinemia, and abnormal neoplastic growth of the gastric mucosa, leading to hyperplasia and possibly dysplasia of the gastric epithelium, specifically affecting the neuroendocrine cells and thus possibly leading to the development of neuroendocrine neoplasms. We argue that a multifactorial concert may play a role in the malignant transformation of hypertrophic and hyperplastic neuroendocrine cells, influenced by genetic predisposition, exposure to environmental factors, and probably differences in the composition of the gastrointestinal microbiota. To date, these risk factors are not well understood, but their identification will be essential for tailored follow-up of patients with AIG to ensure early diagnosis of malignant transformation, consistent with the aim of this study. The authors have added a reference to what is presented here in the Discussion section, page 13.

I confirm that the paper has not been submitted to another journal and that it has not been published in whole or in part elsewhere previously.

Sincerely

Sara Massironi, MD, Ph.D.,

Division of Gastroenterology, Fondazione IRCCS San Gerardo dei Tintori, Monza, Italia

University of Milano-Bicocca School of Medicine, Monza, Italy.

Mail: sara.massironi@libero.it