Author’s response to reviews

Title: Small Bowel Adenocarcinoma As a Complication of Celiac Disease: Clinical and Diagnostic Features

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Version: 1 Date: 19 Feb 2019

Author’s response to reviews:

Ferrara, February 20th, 2019

Dr. Cecilia Devoto, BSc, MSc, PhD
Editor BMC Gastroenterology

Dear Dr. Devoto,

On behalf of my co-authors, please find attached the revised version of our paper entitled: “Small Bowel Adenocarcinoma As a Complication of Celiac Disease: Clinical and Diagnostic Features” BMGE-D-18-00689, which I re-submit along with a thorough point-by-point rebuttal to each comment raised by the two Reviewers (see below).

We would like to thank the Reviewers and the Editorial board for the thoughtful and constructive comments, which helped us to improve the quality our work.
The main comments were only directed to tone down the excess of emphasis of our conclusions (based on the single center experience) on celiac-disease-related small bowel adenocarcinoma (SBA).

We hope that the revised version of our paper is now acceptable for publication in BMC Gastroenterology.

I wish to thank you for your consideration to our paper and look forward to hearing from you in the due course.

Kind regards,

Roberto De Giorgio

Reviewer reports and Reply to Reviewers:

Thomas Aparicio (Reviewer 1): It is an interesting cases reports of 5 SBA occurring in coeliac disease.

Despite the small number new findings are reported with these well describe cases

Reply: We wish to thank Dr. Aparicio for his kind comments and thoughtful assessment of our paper.

Other comments

Title: title is to emphatic. 5 cases could not resume research of millennium
Reply: Absolutely agree. The title has been changed as follows: “Small Bowel Adenocarcinoma as a Complication of Celiac Disease: Clinical and Diagnostic Features”.

Abstract: conclusion should be nuanced as there is only 5 cases

Reply: Agree. The conclusion in the Abstract have been nuanced as follows: “Although in a limited series, herein presented coeliac disease-related SBA cases were characterized by a younger age of onset, a higher prevalence in female gender and a better overall survival compared to sporadic, Crohn- and hereditary syndrome-related SBA”.

Discussion:

1) It is very interesting that even poor prognostic patient (N2) according to the literature have a good prognosis in this study. That should be pointed out

Reply: Absolutely agree. We changed Discussion accordingly with the following sentence: “Notably, it is worth pointing out that cases with advanced CD-related SBA (including the three cases with N2) showed an overall long survival.”

2) The author recommend investigation for patient with CD to detect SBA. According to the low rate of SBA in CD (despite an elevated relative risk), the doubtfull about the adenoma to carcinoma sequence, the fact that in this study the majority of the cases had concomittent diagnosis of CD and SBA, and the lack of standardized repeated screening procedure it is difficult to made any recommendation about screening.

Reply: We agree with the Reviewer that imaging techniques should be cautiously recommended to CD patients. However, the point that we made in the manuscript was about the presence of alarm symptoms / manifestations (e.g., vomiting, FOB, weight loss), which in CD patients treated with gluten deprivation, should, in our view, deserve a thorough diagnostic evaluation. Because of the current structure of the sentence (see Discussion page 12, 2nd para, lines 9-12) we humbly think that the text should not be changed.

Reply: Agree. However, just for the sake of clarity, we never mentioned that SBA associated with Crohn is located in the duodenum. In addition references by Palascak-Juif et al has been appropriately quoted (ref #6).

4) It is unclear that the new diagnostic tools allowed early diagnosis and better prognosis. A recent european study did not find a significant improvement of diagnosis and prognosis of SBA (Legue L, Acta Oncol 2016).

Reply: We take the Reviewer’s comment. A sentence and the suggested ref have been added: “However, a recent population-based study showed that the diagnostic implementation of new techniques did not yield significant advantage in terms of early diagnosis and better outcome (34).” See page 14, last para from top, lines 3-5.

5) Overall conclusion should be nuanced as it is difficult to draw robust findings from 5 cases

Reply: Agree. The concluding sentence has been toned down: “Taken together our data contributed to define some findings of SBA in CD and therefore to expand current knowledge on these patients.” See page 15, Conclusions, lines 9-10.

Reviewer 2 (Reviewer 2): PEER REVIEWER ASSESSMENTS:

Reply: We wish to thank the Reviewer for her/his kind comments to our paper.
Yes - there is a clear objective

DESIGN - Is the current approach (including controls and analysis protocols) appropriate for the objective?

Yes - the approach is appropriate

EXECUTION - Are the experiments and analyses performed with technical rigor to allow confidence in the results?

Yes - experiments and analyses were performed appropriately

Statistics - Is the use of statistics in the manuscript appropriate?

Yes - appropriate statistical analyses have been used in the study

INTERPRETATION - Is the current interpretation/discussion of the results reasonable and not overstated?

Yes - the author's interpretation is reasonable

OVERALL MANUSCRIPT POTENTIAL - Is the current version of this work technically sound? If not, can revisions be made to make the work technically sound?

Yes - current version is technically sound

PEER REVIEWER COMMENTS:

GENERAL COMMENTS: This is an interesting article, relating to an important but rare complication of coeliac disease. The review is limited by the small number of cases of adenocarcinoma, but this is inevitable in such a rare condition. The authors have recognised this limitation.
The comparison of their findings with other similar but smaller cases studies is interesting and well written.

ADDITIONAL REQUESTS/SUGGESTIONS:

The only other possible addition would be in the conclusion section, to mention the hypothetical causes of small bowel adenocarcinoma in coeliac disease; this would include genetic predisposition, the imposed dietary changes which may predispose to cancer (low fibre etc) and changes in the gut microbiome.

Reply: We take the Reviewer’s comment to add to the Discussion the interesting topics he/she raised up. However, for the sake of clarity, none of these hypothetical causes have found any support from published data. Mentioning these etiopathogenetic factors would generate misunderstanding. For example, in our manuscript we stated that conversely to intestinal lymphoma, there is no genetic background (“predisposition”) for small bowel adenocarcinoma (SBA).

Conversely the improved prognosis in this cohort may reflect the ongoing healthcare access and monitoring of this cohort, related to their coeliac disease.

Reply: Agree. We added the following sentence in the text: “The relatively favorable prognosis of CD-related SBA in our series may reflect the cautious follow-up of CD patients in the healthcare system.” See page 15, Conclusions, lines 3-4.