

April 3, 2019

Ruo-Yu Ma

Science Editor, Editorial Office

Baishideng Publishing Group Inc.

Re: Manuscript Revision (World Journal of Gastroenterology No 46346)

Dear Editor,

Thank you for the Editor and Reviewers for considering our manuscript "Upper Gastrointestinal Tract Involvement of Pediatric Inflammatory Bowel Disease: A Clinicopathological Review."

We have made some revisions based on the reviewers' suggestions. The response for each question or suggestion is listed below. The changes in the manuscript are highlighted in yellow. We hope you will find the revised manuscript acceptable for publication. Thank you again.

Sincerely,

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Editor

1. Audio Core tip – **added (separate file)**
2. Decomposable figure of all the figures – **added (separate file)**
3. Manuscript No – **added in the manuscript (highlighted in yellow)**
4. Running title – **added in the manuscript (highlighted in yellow)**
5. Author contributions – **added in the manuscript (highlighted in yellow)**
6. Supported by – **added in the manuscript (highlighted in yellow)**
7. Conflict-of-interest statement – **added in the manuscript (highlighted in yellow)**
8. Telephone/fax – **added in the manuscript (highlighted in yellow)**
9. Core tip – **added in the manuscript (highlighted in yellow)**
10. All authors' abbreviation names and manuscript title – **added in the manuscript (highlighted in yellow)**
11. Title and subtitles format – **modified in the manuscript**
12. Reference format – **modified in the manuscript**

Reviewer 1

1. Dear Editor, I read this manuscript and I think that: - The influence of these conditions on cardiovascular system should be discussed. Please consider the paper from Gesualdo M et al. J Cardiovasc Med (Hagerstown). 2016 May;17(5):330-8. - The authors should include a table gathering the main findings from literature.

Dear Reviewer 1, thank you for your kind suggestion. We agree that cardiovascular manifestations are important to discuss in inflammatory bowel disease. However, we humbly disagree that it should be included in our review as the manuscript emphasizes on the pathology aspect of the upper gastrointestinal tract involvement. Moreover, our focused patient population is children which usually do not demonstrate cardiovascular manifestations. We believe it is more relevant to be discussed in a review paper for adult patients.

Reviewer 2

1. The abstract should better be structured and expanded to be able to stand alone regardless the article.
Dear Reviewer 2, thank you for your constructive criticism. We have modified the abstract to incorporate the reviewers' suggestions. We hope you will find it acceptable. The abstract is highlighted in yellow.
2. A review of literature usually includes more references. Only 41 references is few for a review article.
We have added several references based on the other reviewers' suggestions. The limited number of references is due to the limited number of literature

available regarding this topic. In addition, the manuscript is considered a mini-review.

3. The figures should be cited by their source references.

The figures were captured and obtained by the authors. Therefore, no references required.

Reviewer 3

This review aimed to present the pathological lesions of the upper gastrointestinal tract in pediatric IBD. The content of the manuscript is generally of good quality and useful for the clinician. Pathologists should also benefit from this review, as it points out some important pitfalls. Data regarding oesophageal involvement, focally enhanced gastritis and duodenitis are well presented, mentioning the pertinent references. Figures are illustrative and of high quality.

MAJOR COMMENTS:

1. Abstract: IBD-Unclassified it is not mentioned at all. Pathological lesions are used to classify IBD subtypes in children with IBD. This review should consider the paper by "Liron Birimberg-Schwartz, et al; on behalf of the Pediatric IBD Porto group of ESPGHAN: Development and Validation of Diagnostic Criteria for IBD Subtypes Including IBD unclassified in Children: a Multicentre Study. Journal of Crohn's and Colitis 2017".

Dear Reviewer 1, thank you for your kind suggestions and providing the references for these points. We have altered the abstract to include IBD-U.

2. Abstract should clearly present pathological features encountered in pediatric IBD.

Abstract has been modified to present the pathological features more clearly.

3. Non-caseating epithelioid granuloma should be emphasized more, not just briefly mentioned in the end of the abstract, as it has great diagnostic value.

Abstract has been modified to include and emphasize epithelioid granulomas.

4. There are English errors (grammar and spelling), as throughout the paper, which should be corrected.

Abstract has been modified to correct these errors.

5. Key-words: "non-caseating granuloma" is not included.

Included in the keywords.

6. Introduction: IBD-U should be included (please see above)

The subgroups of IBD according to IBD Porto group of ESPGHAN have been included in the introduction.

7. Paragraph about epidemiology used very old references. There are very recent ones and they should be used, including the paper published in the World journal of gastroenterology: Sýkora J, et al. Current global trends in the incidence

of pediatric-onset inflammatory bowel disease. WJG 2018 (other suggestions: Benchimol EI, et al. Trends in Epidemiology of Pediatric Inflammatory Bowel Disease in Canada: Distributed Network Analysis of Multiple Population-Based Provincial Health Administrative Databases. Am J Gastroenterol. 2017; Saeed SA and Kugathasan S. Epidemiology of Pediatric Inflammatory Bowel Disease. Pediatric Inflammatory Bowel Disease 2017).

The epidemiology has been updated using recent literatures.

8. Some references are strangely cited – as a group, instead of mentioning the authors (i.e. ref. 5, 7, 13, 14)

The references have been corrected.

9. Table 1: references used should be mentioned; prevalence and description of non-caseating granuloma should be inserted, as well as its role in contributing to the final diagnosis of CD (References de Bie C, et al. IBD 2012; Kovacs M, et al. JCC 2012; de Bie C, et al. JPGN 2012; Paerregaard A. IBD 2009). Also, other pathological conditions showing non-caseating granuloma should be mentioned in the Table, including chronic granulomatous disease, emphasizing the importance of differential diagnosis.

The table has been updated to include non-caseating granulomas.

10. Conflict-of-interest statement is missing.

Conflict-of-interest statement has been added.

Reviewer 4

This MS provides a clear and focused overview of the histological features of upper gut involvement in IBD SPECIFIC COMMENTS:

1. There are certainly data to indicate that the inclusion of upper gut biopsies provides much more than "occasional" guidance in diagnosing IBD and in differentiating between CD and UC.

Dear reviewer 4, thank you for your kind comment and suggestions. The statements in the introduction and abstract have been modified.

2. IBDU was not mentioned in the sub-types of IBD

IBD-U has now been included in the abstract and introduction.

3. Although the presence of granulomata was mentioned, this came across as almost an after thought. it would be helpful to mention this more prominently - as the presence of granulomata would be helpful

The manuscript has been modified to emphasize on granulomas (included in Table 1 as well).

4. The Figures have some arrows. It may be helpful to enhance these further to clearly highlight the key findings

The arrows have been enhanced.

5. Table 1 includes prevalence rates but no references

References are included in the table now.

6. In more than 6 occasions referencing is incorrect. When giving an author name followed by et al, the reference should follow immediately after et al (and not at the end of the sentence)

The references have been corrected.

7. There are some errors of English language that need correction

The errors have been corrected throughout the manuscript.