

Dear Editors & Reviewers,

Thank you for your review and comments regarding our proposed manuscript: “Colonic ulcerations may predict steroid-refractory course in patients with ipilimumab-mediated enterocolitis”. Your comments have helped improve the quality of the work. Enclosed below are detailed responses to the comments and all changes to the manuscript from the prior draft. Please do not hesitate to contact us with any additional question or concerns.

RESPONSES TO REVIEWER COMMENTS:

(all are highlighted in the manuscript document)

1. Comment from Reviewer #1: “A minor comment is that on page 6 para 1 (Under Introduction) Line 6 the words 'that patient population' should state 'patients with metastatic melanoma' since this is the first reference in the main body of the paper”
 - RESPONSE: clarified language regarding the patient population for initial melanoma studies (Page 6, paragraph 1, Introduction section).

2. Comment from Reviewer #2: “The authors should specify what is grade 2 diarrhea”
 - RESPONSE: clarified definition of grade 2 or worse diarrhea (Page 8, Results). Please note, the definition of diarrhea grading, including grade 2 and worse, is already provided in the Materials and Methods section.

3. Comment from Reviewer #2: “In the workup the authors should specify the name of “...routine enteric pathogens,..”.”
 - RESPONSE: clarified the enteric pathogens that were tested (Page 9, Workup & Endoscopic findings subsection).

4. Comment from Reviewer #2: "Have the authors data about a potential celiac disease of these patients."
 - RESPONSE: clarified that we do not have data on celiac disease (Page 9, Workup & Endoscopic findings subsection).

5. Comment from Reviewer #2: "In the section discussion the authors should add the fact that "ipilimumab-mediated enterocolitis" is a part of a wide spectrum of "biologics-mediated enterocolitis". A recent review (The pathologic galaxy modulating the genotype and phenotype of inflammatory bowel disease: co-morbidity, contiguity, and genetic and epi-genetic factors. Minerva Medica 2016;107-401-12) highlights the fact that these cases of paradoxical inflammatory bowel disease or IBD (these drugs are usually used to cure IBD) can be explained by recalling that all of these biological formulations can favor specific lymphocyte subpopulation imbalances at the mucosal level."
 - RESPONSE: Reviewer 2 provides helpful comments regarding the spectrum of biologic mediated enterocolitis. While we don't typically think of ipilimumab-mediated enterocolitis as "paradoxical IBD", the reviewers points about the role of potential lymphocyte subpopulations is important. We have added a section to the discussion section addressing these issues, including a brief discussion regarding mechanism of this phenomenon, as well as gaps in our current knowledge. We hope this helps increase the depth of the discussion and addresses the reviewer's comments - if additional clarification or discussion is needed, please let us know (Page 13-14, Discussion Section).

ADDITIONAL EDITS TO MANUSCRIPT:

(all are highlighted in the manuscript document)

6. Page 1, Title Page: added ESPS manuscript number, added “original article” as manuscript type, removed the “SUPPORT” statement since there was no direct support for this project/manuscript.
7. Page 4, Abstract: METHODS – increased detail regarding methods as requested.
8. Page 4, Abstract: RESULTS – increase detail and depth of results as requested.
9. Page 15-16: Added COMMENTS section, including background, research frontiers, innovations & breakthrough, applications & terminology.
10. Page 17-18: References – added PMID to all citations. *Please note, new reference #13 does not have a DOI listed online or in Pubmed, so only PMID is cited.
11. ADDITIONAL FILES: as requested the following files are being submitted with our revised submission: Scientific Process Letter, Audio Core Tip

Sincerely,

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