

16. August. 2021

Dear Editor,

I have received your decision letter on our manuscript entitled **“Celiac disease and malignancies”**. I would like to thank you for giving me the opportunity to revise my manuscript and I appreciate the reviewers’ constructive comments. I have revised my manuscript according to these comments and submitted “highlighted” version of my revised manuscript.

Best regards,

Dr. Kaan Demiroren

### **Responses to the Reviewers’ Comments**

**My answers to the recommendations of the reviewers are respectively as follows:**

The article is well written but needs some improvement:

- 1. Title: the title reflects the main subject/hypothesis of the manuscript.**
- 2. Abstract. the abstract summarizes correctly the work described in the manuscript.**
- 3. Key words. The key words reflect the focus of the manuscript.**

*Thanks.*

- 4. Background. the introduction of the manuscript describes the background of coeliac disease but not the relation with malignancies. Thus the introduction section needs to through some light on refractory coeliac disease and the risk of malignancies.**

*It was added to the introduction as highlighted.*

- 5. Methods. The author needs to give some information on the method he used to search and analyze the data. Did he perform search in pubmed or other sources...etc...?**

*It was added to the introduction as highlighted.*

6. Important points on the text:

**1. The presence of aberrant T cells is necessary for diagnosis of RCD-II. These cells are characterized by the presence of intracellular CD3 and absence of surface CD3 markers. For the diagnosis of RCD-II, T-cell flow cytometry of duodenum biopsies is needed , not only TCR gamma rearrangement. This point needs further clarification under section 2 (Ref CeD).**

*It was added to under the heading "REFRACTORY CELIAC DISEASE" as highlighted.*

**2. A short overview over management of RCD-II and the effect of that on the prevention of EATL is needed. This is essential because of the link between RCD-II and EATL.**

*It was added to under the heading "REFRACTORY CELIAC DISEASE" as highlighted.*

**7. Illustrations and tables. Figure 1 suggests that mere presence of active enteropathy after 1 year in symptomatic pt is RCD. Here should clarified that a negative serology is needed. Otherwise patients with delayed response (slow responders) will be wrongly labeled as RCD.**

*Information that "serology is negative" was added to Figure 1.*

**8. References. Reference to landmark and important references is needed. These references give an account on the criteria of diagnosis of RCD, its treatment options and prognosis, especially: 1. Verbeek WH, et al . Flow cytometric determination of aberrant intra-epithelial lymphocytes predicts T-cell lymphoma development more accurately than T-cell clonality analysis in Refractory Celiac Disease. Clin Immunol. 2008 Jan;126(1):48-56. doi: 10.1016/j.clim.2007.09.002. 2. Al-toma A, et al. Autologous hematopoietic stem cell transplantation in refractory celiac disease with aberrant T cells. Blood. 2007 Mar 1;109(5):2243-9. doi:**

10.1182/blood-2006-08-042820 3. Al-Toma A, et al. Survival in refractory coeliac disease and enteropathy-associated T-cell lymphoma: retrospective evaluation of single-centre experience. Gut. 2007 Oct;56(10):1373-8. doi: 10.1136/gut.2006.114512.

*These 3 references were added as highlighted.*

**9. Quality of manuscript organization and presentation. the manuscript is well written, concise and coherently organized and presented. English language is accurate.**

*Thanks.*

I thank the reviewers for these constructive comments.