Peer Review File

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Reviewer A

This is an interesting narrative review article by Montorsi et al. This article must add useful knowledge for the reader. I have a few minor comments for the authors.

1. In page 1 line 40, "celiac" should be revised as "coeliac".
Reply 1: Thank you for your remark.
Changes in the text 1: "Coeliac disease (CD) is a chronic immune-mediated enteropathy that affects about 1% of the Western population, with a global prevalence that is gradually increasing."

2. In the Table, abbreviations should be spelled out on the first appearance.
Reply 2: Thank you for your remark
Changes in the text 2: We modified the Tables properly

Reviewer B

The manuscript reviews the association of celiac disease with gastrointestinal cancer, including lymphoma.
This manuscript, written by Dr. Montorsi, review type, with the title of "Association between coeliac disease and gastrointestinal cancers: a narrative review" describes the association of celiac disease with gastrointestinal cancer, including lymphoma
The authors stated that it is a systematic review.

1- Regarding the selection of the manuscripts. Did you use the PRISMA guidelines? I would recommend using the PRISMA flow diagram.
https://prisma-statement.org/prismastatement/flowdiagram.aspx

Reply 1: Thank you for your remark. We properly report it. However, the review is a narrative review as stated in the title.
Changes in the text 1: see Figure 1

2- When searching articles, why "lymphoma" keyword was not included?
Reply 2: Thank you for your comment. The keyword "lymphoma" was not included because

the research was focused on GI neoplasm in general. If we included the keyword "lymphoma", which is a type of GI tumors, we should have also included keywords for all the other types of GI tumors (adenocarcinoma, GI NET, GIST, squamous cell carcinoma, etc).
Changes in the text 1: None

3- Did you try to analyze the association of celiac disease with cancer using forest plot?
https://uk.cochrane.org/news/how-read-forest-plot
Reply 3: Thank you for your comment. The proposed review is a narrative review as stated in the title. In this case does not appear appropriated any statistical analyses.
Changes in the text 3: None

I also add the link of Cochrane:
https://community.cochrane.org/help/tools-and-software

You may use RevMan
https://training.cochrane.org/online-learning/core-software/revman

4- The pathogenesis of celiac disease is not described. I think the manuscript would benefit from more insights in celiac disease. There are many review and research publications.
You could use this one:

Carreras J. Artificial Intelligence Analysis of Celiac Disease Using an Autoimmune Discovery Transcriptomic Panel Highlighted Pathogenic Genes including BTLA. Healthcare. 2022; 10(8):1550. https://doi.org/10.3390/healthcare10081550

Reply 4: Thank you for your remark. We agree with you that adding the pathogenesis of coeliac disease would be a benefit for the present article.
Changes in the text 4: "CD is characterized by small intestinal mucosal inflammation and villous atrophy in patients who have higher sensitivity of the immune system to gluten of the diet and to gluten-related proteins. As many autoimmune disorders, CD occurs in patients who are genetically predisposed. Indeed, the almost all the patients have HLA DR3-DQ2 and/or the DR4-DQ8 in their genome and the belief that other non-HLA locus genes such as REL, MICA, CTLA4, MMP3, MIF, TNFAIP3 (A20), NKG2D may also be involved in the disease pathogenesis is getting stronger. The main mechanism of inflammation is driven by the reaction of the intestine to gliadin fraction leading to inflammation of the lamina propria and epithelium and subsequent disruption of the epithelial layer and villous atrophy. Both innate and adaptive immune response play a key role with the activation of gliadin reactive T cells,

autoantibodies, intraepithelial lymphocytes, macrophages, monocyte, and dendritic cells."

5- The association, multistep process between celiac disease, refractory celiac disease I and II, and EATL type 1 could be explained with more detail.
Please remember that the "accepted" evolution is from refractory celiac disease type II (monoclonal) towards EATL type I.
Nowadays, EATL type II is called MEITL.

Enteropathy—associated T—cell lymphoma (EATL), previously designated type I EATL, is a neoplasm of intraepithelial T cells that occurs in individuals with coeliac disease and exhibits varying degrees of cellular pleomorphism. It commonly presents as a tumour composed of medium—sized to large lymphocytes, often accompanied by a component of chronic inflammatory cells. The adjacent small intestinal mucosa shows villous atrophy, crypt hyperplasia, and increased intraepithelial lymphocytes. Lymphomas composed of monomorphic mediumsized cells (formerly called type II EATL) are now considered to constitute a distinct entity (monomorphic epitheliotropic intestinal T—cell lymphoma).
[WHO2016]

Definition
Monomorphic epitheliotropic intestinal T—cell lymphoma (MEITL) is a primary intestinal T—cell lymphoma derived from intraepithelial lymphocytes. Unlike in the classic form of enteropathy-associated Tcell lymphoma (EATL), there is no clear association with coeliac disease {3850}. The neoplastic cells have medium—sized round nuclei with a rim of pale cytoplasm. There is usually florid infiltration of intestinal epithelium. An inflammatory background is absent, and necrosis is usually less evident than in classic EATL. Based on distinctive pathological and epidemiological features, and to facilitate distinction from EATL, this disease is no longer referred to as type II EATL.
[WHO2016]"

Refractory celiac disease — Some cases of enteropathy associated T cell lymphoma (EATL) are preceded by a low-grade precursor lesion that clinically resembles refractory celiac disease (refractory sprue). Refractory celiac disease is clinically defined as the persistence of pathologic changes in the intestine consistent with celiac disease despite a strict gluten-free diet for more than 12 months. These pathologic changes include increased intraepithelial lymphocytes, villous atrophy, and crypt hyperplasia. (See "Diagnosis of celiac disease in adults", sectionì' on 'Endoscopy with small bowel biopsy' and "Management of celiac disease in adults", section on 'Refractory sprue'.)

Cases of refractory celiac disease are commonly divided into two types:

Type I refractory celiac disease – These lesions typically show no atypia in the intraepithelial lymphocytes, normal surface T cell receptor, CD3 and CD8 expression by intraepithelial T lymphocytes and a polyclonal pattern on T cell receptor gene rearrangement studies [4].

Type II refractory celiac disease – These lesions also have no atypia in the intraepithelial lymphocytes, but demonstrate a loss of surface T cell receptor, CD3, or CD8 expression and may have a monoclonal T cell receptor gene rearrangement [29,34].

The clinical significance of refractory celiac disease type is incompletely understood. While type I refractory celiac disease is unlikely to progress to EATL, type II may be a precursor lesion to EATL. Imaging with computed tomography, positron emission tomography, and video capsule endoscopy may help to identify cases of refractory celiac disease that have progressed to EATL [35-37].

Replay 5: Thank you for your remark. We properly modified the paper
Change in the text 5: "EATL is an aggressive form of NHL of the gut, which accounts for only 5% of all gastrointestinal lymphomas54–56 and characteristically arises when refractory CD occurs. EATL is commonly characterized by medium-sized to large lymphocytes together with component of chronic inflammatory cells. When this lymphoma is characterized by the presence of monomorphic medium-sized cells constitute a distinct entity which was classified as EATL type 2 and now is called monomorphic epitheliotropic intestinal T—cell lymphoma (MEITL). No association between MEITL and CD has been demonstrated. EATL is usually characterized by a multifocal involvement mainly of the jejunum, and in other cases, the remaining GI tract is involved37. Refractory CD (RCD), which can be considered a low-grade precursor lesion that clinically resembles refractory celiac disease, is defined as persistent or recurrent symptoms and signs of malabsorption with villous atrophy despite a strict GFD for at least months54,57, and it can be classified as type one and two. RCD type 1 and 2 are both characterized by lesions with no atypia of intraepithelial lymphocyte. The main difference between the type 1 and 2 are the presence of normal surface T cell receptor, the expression of both CD3 and CD8 by intraepithelial T lymphocytes and the presence of a polyclonal pattern on T cell receptor gene rearrangement studies which can be found only in type 1 RCD. Indeed, RCD type 2 is characterized by loss of surface T cell receptor, CD3 or CD8 expression and the presence of a monoclonal T cell receptor gene rearrangement. While type I RCD is unlikely to progress to EATL, type II may be a precursor lesion to EATL."