Reply to reviewers

Dear Editor-in-Chief,

Dear reviewers,

Thank you for evaluating our manuscript and for the valuable comments made in your review notes. We have addressed all your remarks on a point by point basis and made changes throughout the manuscript accordingly. We have followed the Criteria for Manuscript Revision and changed the manuscript type as Case Report. Also, to increase the language quality we used a professional proofreading service to check the manuscript. Please find attached the revised version of the manuscript.

Reviewer comment

- "In the circle of related-autoimmune diseases, celiac disease (CD) and Sjogren's syndrome (SS) come together with type 1 diabetes mellitus (DM), autoimmune thyroid disease (ATD) and primary biliary cholangitis (PBC)." Cite a reference - "Moreover, the importance of extraintestinal manifestations and of clinical associated conditions has been increasingly recognized" Cite, for example, "Epilepsy and celiac disease: review of literature. Panminerva Med. 2011 Dec;53(4):213-6."

Authors' reply

Thank you for the reference suggestion. We have added 4 references in support of the text above – regarding associated autoimmune disorders and extraintestinal manifestations of CD, including the one recommended in your comment.

Reviewer comment

- "We decided to perform an upper gastrointestinal endoscopy" Why did you perform endoscopy without waiting for antibodies results?

Authors' reply

Thank you for the comment. We performed the endoscopy along with the serological testing because of the clinical suspicion of CD (patient with associated autoimmune disorder, iron deficiency) and taking into consideration the possibility of seronegative CD.

Reviewer comment

The authors describe a case of a patient with known Sjogren's syndrome who was found to have coeliac disease on gastroscopy when being evaluated for a cause of iron deficiency. The iron deficiency and villous atrophy resolve with a gluten free diet. The authors then provide a short review of potential associations between coeliac disease and Sjogren's syndrome and suggest that the association may be more than just related to the two conditions being autoimmune, although then evidence to support this are limited. The suggestions are presented in a clinically relevant manner, but I think the major issue with the study is that it acknowledges the limitations of the literature but does not provide sufficient evidence to support the purported strong association nor suggestions of how to overcome the deficiencies in the literature for clinicians, which is how this case would be useful.

Authors' reply

Thank you for pointing out this issue in our paper. In the revised form of our manuscript, we have expanded the discussion section accordingly, emphasizing the lack of strong data in the literature on the association of CD and SS and the scenarios when clinicians should keep a high index of suspicion for CD in a SS patient.

Reviewer comment

I have the following suggestions: 1. The review of prevalence is rather superficial. The specific qualities of the studies that report high prevalence versus low prevalence should be compared so that a meaning conclusion can be reached as to which is more realistic. Some of the studies reported no difference from the general population in rates of celiac disease amongst those with SS and further discussion is required.

2. In the section on autoantibodies and pathophysiology, while the genetic loci are discussed, the immunological significance of this to both conditions needs to be discussed to provide some justification for the belief that both conditions are related.

3. The section on future direction needs to clarify how sensitive each of the screening tests are and which ones should be used. There needs to be some discussion of whether false positive tests can occur more frequently as the authors have discussed

in the antibody section. Discussion of the suggested screening tests should be added to Table 3.

Authors' reply

Thank you for these constructive suggestions. We have critically analyzed the prevalence studies selected in the literature review according to the population tested and diagnostic tests used, and we formulated remarks about the difference in prevalence amongst selected papers – this has been incorporated in the revised discussion section. Also, further details on the immunological background of the two conditions are provided in the revised version of the manuscript, as suggested. Not least, diagnostic accuracy of tests recommended for screening has been added in the discussions.

Reviewer comment

Minor points: - Normal ranges should be reported for all laboratory results - Were TTG levels above the upper limit of the test performed or was a value given? If so, this should be reported - Table 3 – change "search for" to "consider". - The title of the last section – consider changing "agenda" to "direction"

Authors' reply

We have provided results of tests with patient's value and range within brackets. Also, we have made changes in Table 3 and the title of the last section according to your suggestions.

Reviewer comment

This is a well written review about the association of Sjogren syndrome with celiac disease. A case is presented followed by literature search. Celiac disease is associated with autoimmune diseases; type 1 diabetes and thyroiditis are the most known ones. As the paper indicates, although the association of these two entities is known, it is not a common practise to evalute these patients regarding this association.This paper may further raise awareness about this issue and enable to conduct large scale studies both in children and in adults.

Authors' reply

Thank you for your feedback on our paper. Indeed, there is a need to increase awareness on the association of the two diseases, both amongst clinicians and researchers.

Reviewer comment

Autoimmune disease may present together . There is no any additional information regarding this topic.

Authors' reply

Although the association of the two autoimmune diseases is known, currently available guidelines are not reporting it. Also, to our knowledge, this is the first review of the literature on the association of CD and SS. We bring in front of the readers a clinical scenario in which screening for CD should be sought of, and provide insight on how this association should be considered in routine practice.

Reviewer comment

In this manuscript that is a case report with revision of literature. (Why do you consider it a review?) Authors aimed to summarize the existing data about association CD and SS, with its implications in clinical practice. It is worth their effort to raise the awareness of the association between CD and SS among internal medicine specialists, rheumatologists and gastroenterologists. Authors describe a clinical vignette: woman 39 yrs old without upper GI symptoms, low serum iron, ferritine unclear (which were the normal values?), Hb in physiological range, normal menses (what does it mean?) However, I do not understand why she underwent upper GI endoscopy before performing at least IgA total and antitranslutaminase IgA. In fact "Of all the serological tests, IgA anti-TG2 Ab is the most widely used test both for the diagnosis and initial screening for CeD because of its very high sensitivity and specificity, ease of use, and its quantitative capability. In a recent systematic review, Chou R et al. reported a pooled sensitivity of anti-tTG Ab to be 92.8% (95% CI, 90.3–94.8%); specificity 97.9% (95% CI, 96.4–98.8%); a positive likelihood ratio (LR) of 45.1 (95% CI, 25.1–75.5%) and negative LR of 0.07 (95% CI, 0.05–0.10%) ["Chou R.; Bougatsos C.; Blazina I.; Mackey K.; Grusing S.; Selph S., authors. Screening for Celiac Disease:

Evidence Report and Systematic Review for the US Preventive Services Task Force. JAMA. 2017;317:1258–1268. ” Furthermor, Authors stated the need of serological screening in the next part of the manuscript. Consequentely, the reason to perform an upper GI endoscopy should be explained. It should be stated that IgG- anti-deamidated gliadin peptide antibody together with IgG-TG2 are regarded as the best tool for identifying CD in patients with selective IgA-deficiency. Leffler DA, Schuppan D. Update on Serologic Test ing in Celiac Disease. Am J Gastroenterol 2010;105(12):2520 2524. doi:10.1038/ajg.2010.276

Authors’ reply

Thank you for the remarks made in your report. By changing the manuscript type into ”Case report”, we have provided more details on the clinical features, blood work, endoscopy and histology. Regarding the endoscopy, we performed it along with serological testing, because of the high clinical suspicion for CD and considering the possibility of seronegative CD. Currently available guidelines for CD diagnosis in adults state that “the diagnosis of CD relies on a combination of clinical, serological and histopathological findings”; also, as stated in discussions, in patients with autoimmune background disease, the rates of CD-serology false positivity might be increased. We expanded the discussion on serology according to yours and other reviewers’ comments and included the above-mentioned references.

Thank you again for all your comments, which were appreciated and taking into account for this revised, better version of our manuscript.