Peer Review File

Article information: https://dx.doi.org/10.21037/tp-21-342

Reviewer A

Comment 1: In regards to the first endoscopy, did all colonic biopsies show subepethelial collagen bands of 30 μm or only specific areas of the colon?

Reply 1: Thank you for your comment. Yes, all colonic biopsies showed subepithelial collagen bands of 30 μm. We have added this in the text.

Changes in the text: We have revised our text as advised (see Page 6, line 114-116).

Comment 2: In the case, it is stated that "Endoscopy findings, which were conducted one year after the diagnosis of adult-type collagenous gastritis, have improved but histological findings still showed collagen deposits with chronic inflammation in the stomach and colon." What does improved mean? Since the primary endoscopic and histologic findings were described in details, is it possible for comparative reasons be more specific about the follow up endoscopic and histologic findings?

Reply 2: Thank you for your comment. This means that the follow-up EGD, which was conducted one year after the diagnosis of collagenous gastroduodenocolitis, showed improvement of previously observed active ulcers and scars, while diffuse nodularity, and mucosal erythema and erosions were continuously observed. We have added this in the text.

Changes in the text: We have revised our text as advised (see Page 7, line 122-125).

Comment 3: How long was the patient on treatment with PPI and Iron supplements? Was he on them at the one year follow up endoscopy?

Reply 3: Thank you for your comment. Yet, it was continued. We have added this in the text.

Changes in the text: We have revised our text as advised (see Page 7, line 122).

Reviewer B: In this manuscript, Kang et al. present a pediatric case of collagenous gastritis (CG) with concomittant colonic involvement and provide a short review of the current literature. While the case described in this report is not very novel as such, it can be considered valuable to increase the awereness of this rather rare (and most probably underdiagnosed) disease. I have some suggestions/comments below which I hope can be helpful to further improve the clarity of the paper. Considering the rarity of the disease, I consider it especially important to provide a as detailed description of the patient case as possible. Moreover, the findings from two recent publications (Käppi et al 2020; PMID: 32955189 and Beinvogl 2021; PMID: 34173792) should be incorporated in the manuscript, as they are the biggest published cohorts of pediatric CG to date.

Comment 1: Lines 50-51: The diagnostic cut-off of 10 μm that have conventially beeb applied for the thickness of subepithelial collagen layer should not be mentioned just in the abstract, but also in the introduction section.

Reply 1: Thank you for your comment. We agree with your comment. We have added this in the text.
Changes in the text: We have revised our text as advised (see Page 5, line 58-59).

Comment 2: Lines 52-54: There are also other hypotheses that have been suggestested and should be mentioned here. See e.g. Beinvogl 2021 (PMID: 34173792) for summary of proposed mechanisms.
Reply 2: Thank you for your comment. We agree with your comment on the suggested hypothesis that collagen deposition may be the result of a reparative process in response to an earlier inflammatory, autoimmune, infectious, or toxic insult. We have added this in the text.
Changes in the text: We have revised our text as advised (see Page 5, line 60-62).

Comment 3: Line 56: Although the terms pediatric- and adult-type phenotypes have tranditionally been proposed, in the light of the more recent knowledge, the terms isolated CG and CG with concurrent intestinal/colonic involvement may be more appropriate. In some cases, there may be a concurrent collagenous inflammation in the small bowel, too, and this possibility should also be mentioned.
Reply 3: Thank you for your comment. We agree with your comment, and have changed our manuscript to introduce the traditional terms "pediatric- and adult-type" in the earlier part of the discussion and have used the terms of "collagenous gastritis (CG), collagenous gastritis (CG) with concurrent collagenous colitis (CC) afterwards. Moreover, the title of this manuscript was also changed according to this comment. We have also mentioned the possibility of concurrent collagenous inflammation in the small bowel, as in this case.
Changes in the text: We have revised our text as advised (see Page 9-10, line 153-187).

Comment 4: Line 74: For improved clarity, it should be specified whether the ferrous sulphate treatment was given continously or intermittently. The route of administration should also be mentioned.
Reply 4: Thank you for your comment. Treatment with iron was given orally and continuously. We have added this in the text.
Changes in the text: We have revised our text as advised (see Page 6, line 81; Page 7, line 105; line 118; line 122; Page 8, line 130; line 133).

Comment 5: Line 81: It should be specified which inflammatory markers were tested. It would also be valuable to mention whether or not the serum albumin level was normal as hypoalbunemia has been described in some patients with colonic disease.
Reply 5: Thank you for your comment. Inflammatory markers of CRP and ESR were tested. Albumin levels were mildly decreased, and we have added the levels in the text and table 1.
Changes in the text: We have revised our text as advised (see Page 6, line 89-90; Page 7, line 107-108; Table 1).

Comment 6: Lines 82-87: It would be valuable to provide more detailed data on the location of the histological inflammation (both in antrum and corpus in stomach? in all colonic segments or just locally?) Was specific collagen stains performed for biopsies from the first endoscopic evaluation?
Reply 6: Thank you for your comment. Biopsy samples were obtained from both the antrum and body in the stomach, and from all segments in the colon. The first endoscopic biopsies did not reveal any thickened collagen bands and specific collagen stains were not conducted then. Thickened collagenous bands were first revealed on the second endoscopic biopsies and that was when specific collagen statins were first conducted. Only chronic inflammation was noted in the specimens from the first biopsy. However, we later retrospectively conducted a special stain for the biopsies from the first endoscopy, which revealed negative findings for CG. We have added this in the text.
Changes in the text: We have revised our text as advised (see Page 5, line 96-98; Page 11-12, line 207-217).

Comment 7: Line 87: It should be given if there was any other evidence (histology, culture or fecal antigen test) supporting the diagnosis of Hp-gastritis. At least according to the European and North-American concensus guidelines (ESPGHAN/NASPGHAN 2016), a positive CLO test alone is not enough for a definite diagnosis of Hp-gastritis.
Reply 7: Thank you for your comment. Histology was negative for HP. Culture and fecal antigen test was not conducted. We agree with your comment and have revised our manuscript that the diagnosis of Hp-gastritis was not definite but "suspected".
Changes in the text: We have revised our text as advised (see Page 6, line 100; 102; Page 10-11, line 188-195).

Comment 8: Lines 100-101: It should be specified whether or not the colonic collagen deposition was seen in one biopsy/colon segment only. Which part of the colon in that case?
Reply 8: Thank you for your comment. Colonic collagen deposition was observed in all segments. We have added this in the text.
Changes in the text: We have revised our text as advised (see Page 7, line 114-116).

Comment 9: Line 103: Don't the authors consider that the patient had a collagenous duodenitis, too, condidering the endoscopic findings and an increased collagen deposit in duodenal biopsy?
Reply 9: Thank you for your comment. Yes, we agree with your comment, and have added the term "collagenous duodenitis (CD)" in the text, as well as have changed the title using the term "collagenous gastroduodenocolitis".
Changes in the text: We have revised our text as advised (see Page 5, line 70; Page 6, line 117-118; Title).

Comment 10: Line 104: Budesonide has a well-proven effect as a treatment of symtomatic collagenous colitis in adults and some clinical experience indicates the

same applies for children, too. Was that treatment considered in this case?
Reply 10: Thank you for your comment. We agree with your comment. Actually, systemic corticosteroid treatment was attempted between the 2nd and 3rd year follow-up endoscopy. However, his IDA did not improve. We have added this in the text.
Changes in the text: We have revised our text as advised (see Page 8, line 128-131).

Comment 11: Lines 107-108: It would be worth mentioning whether or not the patient's weight gain that was affected initially also improved during the follow-up.
Reply 11: Thank you for your comment. The patients initial weight loss was actually recovered after eradication treatment of suspected H. pylori gastritis. Thereafter, no abnormal weight loss was noted afterwards. We have added in the text that his weight was recovered after eradication treatment.
Changes in the text: We have revised our text as advised (see Page 6, line 102).

Comment 12: Line 122: The estimate of incidence given here is based on compound data from the cases reported in the literature. As there are most propobly many more unreported cases, the reliability of such estimates is uncertain. Methodologically, a more reliable way to estimate the incidence is population-based studies. There is a Scandinavian population-based pediatric study that presents an estimated incidence figure and should be referrenced in this context (Käppi et al 2020; PMID: 32955189).
Reply 12: Thank you for your comment. We agree with your comment and have added the estimated incidence and prevalence in the study of Käppi et al in the text.
Changes in the text: We have revised our text as advised (see Page 9, line 144-146).

Comment 13: Lines 129-131: Please see the earlier comment regarding the the use of terms adult and pediatric phenotype. Furthermore, the classification is normally primarily based on histological findings, and the symtoms just reflect the GI segment that is affected.
Reply 13: Thank you for your comment. We agree with your comment, and have changed our manuscript to introduce the traditional terms "pediatric- and adult-type" in the earlier part of the discussion and have used the terms of "collagenous gastritis (CG), collagenous gastritis (CG) with concurrent collagenous colitis (CC) afterwards. Moreover, the title of this manuscript was also changed according to this comment. We have also revised the text that the classification between pediatric- and adult-type is based on histologic findings.
Changes in the text: We have revised our text as advised (Page 9-10, line 153-187).

Comment 14: Lines 134-135: "The size and number of nodularity depend on the severity of the inflammation…" While this may potentially be true, is there really current evidence to back up this statement? A reference should be provided in that case.
Reply 14: Thank you for your comment. We have provided the reference.
Reference #18. Kamimura K, Kobayashi M, Sato Y, et al. Collagenous gastritis: Review. World J Gastrointest Endosc 2015;7:265-273.
Changes in the text: We have revised our text as advised (see Page 9, line 157-158).

Comment 15: Lines 136-138: "The anemia of pediatric collagenous gastritis is probably a result of these dilated capillaries and gastrointestinal bleeding". This is just one theory that has been proposed. Alternative mechanisms (such as iron malabsorption) have also been suggested (see e.g. Käppi et al 2020; PMID: 32955189) and would be worth mentioning here.
Reply 15: Thank you for your comment. We agree with your comment have revised the text according to your comment.
Changes in the text: We have revised our text as advised (see Page 9-10, line 162-167).

Comment 16: Lines 140-146: For improved clarity for the reader, it would be valuable if the authors brought up the approximate proportions of the pediatric patients with isolated CG vs. those with concurrent intestinal/colonic involvement, respectively. Data on this can be found from recent papers reporting pediatric cohorts (Matta 2018, Käppi 2020, Beinvogl 2021)
Reply 16: Thank you for your comment. We agree with your comment. CG with concurrent CD and/or CC is very rare, and to date there are 24 pediatric cases reported in case reports or in cohort studies (1,2,5–16) including this case (Table 2). Recently, Beinvogl et al have reported the largest cohort of CG in children of 40 patients (2). In this study, concurrent CD was noted in 7/40 (17.5%), CC in 3/40 (7.5%) and ileitis in 1/40 (2.5%). One patient (2.5%) had involvement in the entire GI tract, who had been previously reported in a case report (13). In the second largest pediatric cohort of 15 CG patients reported by Käppi et al, CD was noted in 1/15 (6.7%), and CC in 1/15 (6.7%). Considering that approximately 120 cases of pediatric CG have been reported in literature, cases with pediatric CG with concurrent CD and/or CC comprises approximately 20% of the total cases with pediatric CG (1,2,5-16). Cases of pediatric CGDC as in this case are even more scarce, and to our knowledge there are only six cases including ours, comprising approximately 5% of the total pediatric cases of CG (5,8,9,13,14)
Changes in the text: We have revised our text as advised (see Page 10, line 176-187).

Comment 17: Lines 146-148: The figures regarding the number of reported cases are not up-to-date, as two recent studies are lacking (Käppi et al 2020, Beinvogl 2021). These studies are currently the biggest ones on pediatric collagenous gatritis and should therefore definitely be included in the literature review. Both studies include also patients with concomittant colonic disease.
Reply 17: Thank you for your comment. We have added the cases reported in the two recent studies by Käppi et al and Beinvogl et al. One case of CG with concurrent enteritis and colitis in the study of Beinvogl et al had been previously reported in a case report by the same author. Therefore, this case was cited by the previously reported case report (Reference 13).
Changes in the text: We have revised our text as advised (see Table 2).

Comment 18: Lines 151-163: Although the pathogenesis of CG may be multifactorial,

the current evidence suggests that the vast majority of pediatric CG cases are not associated with H. pylori (Käppi et al 2020: Beinvogl et al 2021). For clarity, this aspect should be mentioned when the authors speculate about the possible role of H pylori in the pathogenesis of CG. Considering the high prevalence of H.pylori in many populations, the concurrent finding of H.pylori and CG may be merely just a coincidence.
Reply 18: Thank you for your comment. We agree with your comment and have added that the concurrent finding of HP and CG may have been merely just a coincidence. We also have deleted the previous table 2 of "Patients Diagnosed with Collagenous Gastritis after Infected with H. pylori".
Changes in the text: We have revised our text as advised (see Page 11, line 202-206).

Comment 19: Lines 165-167: It should be clarified that despite many treatment options that have been tested, an efficient treatment is currently lacking.
Reply 19: Thank you for your comment. We have added this in the text.
Changes in the text: We have revised our text as advised (see Page 12, line 218-219).

Comment 20: Line 181: "Considering that the number of cases with adult-type increases,.." This statement should be backed up by a reference. The current literature of CG consists of case reports and small case series and in my opinion there is currently not really published data to support this statement.
Reply 20: Thank you for your comment. We agree with your comment and have deleted this sentence.
Changes in the text: We have revised our text as advised (see Page 12-13, line 234-240).

Comment 21: Lines 183-184: "Therefore, children diagnosed with collagenous gastritis should also undergo a colonoscopy for the evaluation of collagenous colitis". The authors should motivate this recommendation more closely. Is it truly motivated to perform a colonoscopy also in CG patients without intestinal symtoms? Considering that approximately only 10% of children with CG have a concurrent colonic involvement, 9 out of 10 patients would in that case undergo a colonoscopy without any findings. At the same time, the treatment of collagenous colitis (primarily with budesonide) is normally only motivated if the patient has symtoms. Therefore, a better strategy may be to be observant for intestinal symtoms (such as diarrhea) and perform a colonoscopy in case the symtoms occur.
Reply 21: Thank you for your comment. We agree with your comment and have revised the text according to your comment.
Changes in the text: We have revised our text as advised (see Page 12, line 235-236).

Comment 22: Figures 2 and 3: As many readers may not be very familiar with pathology slides, it would be advisable to use arrows (or other indicator) to clearly point out the location of the collagen layer in the pictures.
Reply 22: Thank you for your comment. We have used arrows to clearly point out the

location of the collagen layer in the pictures.
Changes in the text: We have revised our text as advised (see Figure 2, 3).

Comment 23: Table 1: Data reported by Käppi et al 2020 (PMID: 32955189) and Beinvogl 2021 (PMID: 34173792) are missing and should be included.
Reply 23: Thank you for your comment. He have included data from these two recent studies.
Changes in the text: We have revised our text as advised (see Page 10, line 176-187; Table 2).

Reviewer C: Good summary, no recommendations