Collagenous gastritis: A case report

Kolagenozni gastritis – Prikaz primera

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Abstract

Background: Collagenous gastritis is a rare disease defined histologically by the subepithelial deposition of collagen bands thicker than 10 μm and the infiltration of inflammatory mononuclear cells in the lamina propria. There are approximately 60 reported cases of collagenous gastritis in the English literature.

Case report: We present a 41-year-old female patient with weight loss, postprandial abdominal discomfort, early satiety, flatulence and a change in bowel habits. Her current laboratory investigation reports showed mild sideropenic anemia. Esophagogastroduodenoscopy and the corresponding histological examination showed findings, typical for collagenous gastritis. Gastric emptying scintigraphy and SPECT/CT of the abdomen revealed gastroparesis.

Conclusion: Collagenous gastritis is a diagnostically challenging disease and its exact etiology remains unclear. Even though collagenous gastritis is a histological diagnosis, the combination of other key clinical and endoscopic findings should prompt consideration of this entity. No safe and effective treatment has been established. Therefore, better understanding of the disease and study of a larger number of patients will help to establish diagnostic criteria and therapeutic strategies.

Izvleček

Izhodišča: Kolagenozni gastritis je redka bolezen, pri kateri najdemo v histološki sliki pomnoženo kolagenizirano vezivo pod epitelom (debeline vsaj 10 μm) in monojedrnocelični infiltrat v lamini propriji. V angleški literaturi je do sedaj opisanih približno 60 primerov kolagenoznega gastritisa.

Prikaz primera: V prispevku je prikazan primer 41-letne bolnice, obravnavane zaradi hujšanja, nelagodja po jedi, prezgodnjega občutka sitosti, napenjanja in sprememb v odvajanju blata. Laboratorijski izvidi so razkrili sideropenično anemijo. Izvida ezofagogastroduodenoskopije in pripadajoče histološke preiskave sta bila značilna za kolagenozni gastritis. Scintigrafija hitrosti praznjenja želodca in SPECT/CT trebuha sta pri bolnici odkrili še gastroparezo.

Zaključek: Kolagenozni gastritis je diagnostično zahtevna bolezen, njegova etiologija pa ostaja nepojasnjena. Čeprav je diagnoza kolagenoznega gastritisa histološka, moramo nanjo pomisliti, če odkrijemo ključne klinične in endoskopske znake. Zaenkrat še ne poznamo varnega in učinkovitega zdravljenja. Za oblikovanje diagnostičnih meril in razvoj učinkovitega zdravljenja bi bilo potrebno boljše razumevanje bolezni in raziskave na večjem številu bolnikov.

Background

Collagenous gastritis (CG) is a rare disease defined histologically by the subepithelial deposition of collagen bands thicker than 10 μm and the infiltration of inflammatory mononuclear cells in the lamina propria.[1,2] CG has similar histological characteristics as collagenous colitis and collagenous sprue and are

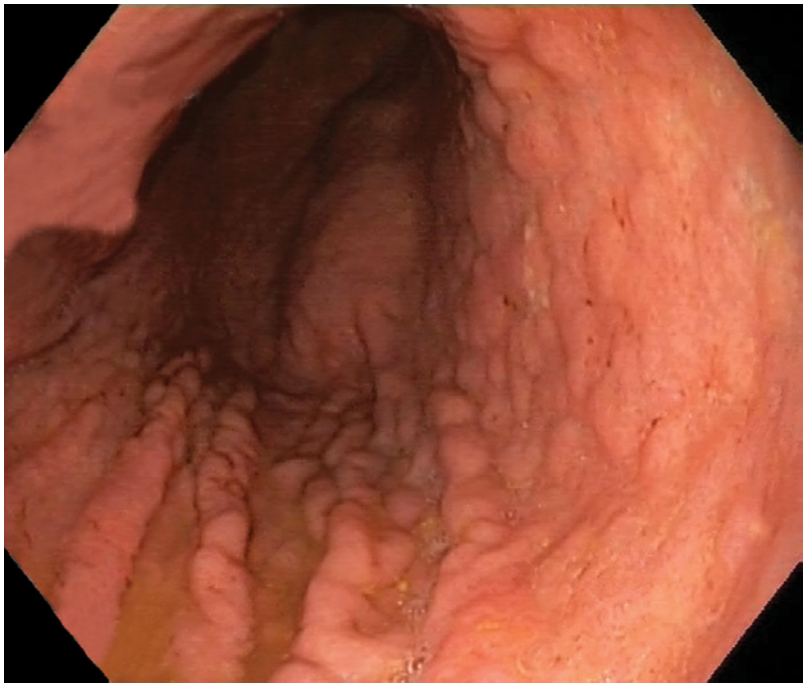

Figure 1: Nodular appearance of the stomach mucosa on gastroscopy.

thought to be part of the same disease entity – collagenous gastroenteritides.[1] While there are many published cases of collagenous colitis, there are only 60 reported cases of CG in the English literature since the disease was first identified by Colletti and Trainer in 1989.[1,3] In contrast to collagenous colitis, the course of CG is unpredictable and the optimal treatment has yet to be defined. We present a patient with CG.

Case report

A 41-year-old Caucasian woman presented with a history of progressive weight loss, postprandial abdominal discomfort, early satiety, flatulence and a change in bowel habits. She has previously been diagnosed with an eating disorder (anorexia nervosa) and has been treated by a psychiatrist with cognitive behavioral therapy. While her treatment was reported successful and she managed to gain some weight and menstrual cycle (although irregular) her other symptoms mainly persisted. She has not been maintained on any pharmacological therapy so far. She was referred to a gastroenterologist for further evaluation.

On examination a decreased body mass index of 16.8 was found. Her laboratory values showed a mild sideropenic anemia. We diagnosed lactose intolerance (low lactase levels in duodenal mucosa and a positive blood lactose tolerance test) and she was given proper diet counseling. We excluded celiac disease and other immune-related disorders. Previously reported elevated total IgE levels were now normal. She underwent esophagogastroduodenoscopy, which showed nodularity (Fig. 1) and oedema of the gastric corpus and antrum. Duodenal bulb mucosa exhibited a diffuse cobblestone appearance. Biopsies were taken from the stomach according to the Sydney protocol and from the duodenum. Histological examination of gastric biopsies showed a thickened subepithelial layer in the corporal and antral mucosa (Fig. 2) with associated gastritis. The inflammatory infiltrate was predominantly lymphoplasmacytic. The subepithelial collagenous layer stained blue with Masson trichrome stain (Fig. 3) and was more than 20 μm thick, suggesting the diagnosis of CG. Immunohistochemistry for *Helicobacter pylori* was negative. Histological examination of the duodenal biopsies showed a non-specific chronic inflammation, but staining with Masson trichrome stain did not show a thickened subepithelial layer of connective tissue. In addition to esophagogastroduodenoscopy, she also underwent colonoscopy: macroscopic appearance of the mucosa was normal, however, histological examination of the biopsy samples showed mild inflammation, but it was not diagnostic for collagenous colitis. Furthermore, we performed gastric emptying scintigraphy and SPECT/CT of the abdomen, which revealed delayed emptying from the fundus and corpus of

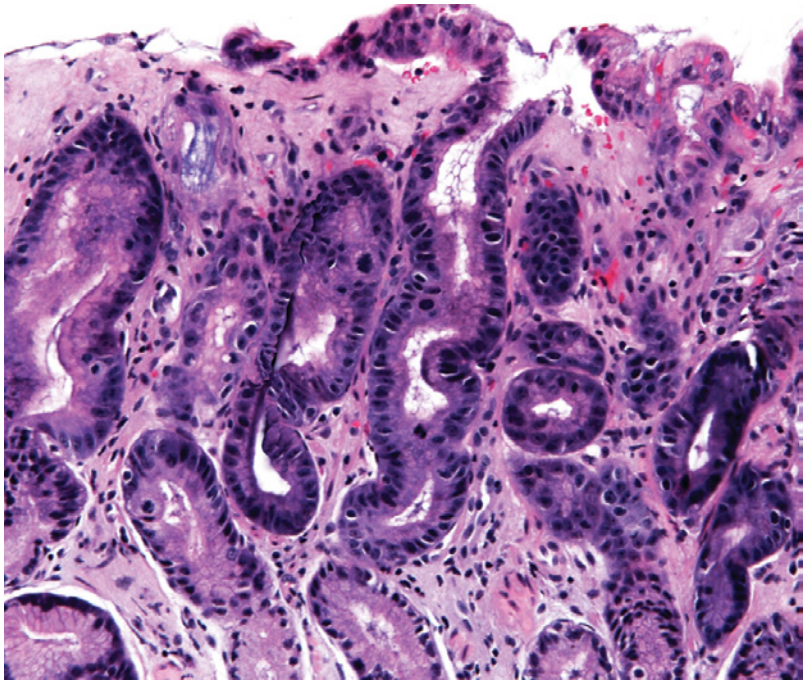

Figure 2: Increased collagenous fibrous tissue beneath the surface epithelium in the biopsy sample from the antral mucosa. Hematoxylin and eosin, orig. magn. 20x.

the stomach, thus suggesting gastroparesis.

After reviewing the literature and excluding all potentially reversible factors, which might influence and/or cause CG (e.g. immune-related disorders, specific drugs), we have decided to start a trial with a proton pump inhibitor for symptom relief. Treatment of sideropenic anemia with oral iron supplements was ineffective, but was resolved after parenteral iron supplementation. Because of suspected gastroparesis she was also started on a short-term therapy with a prokinetic agent: first with metoclopramide and later with domperidone. She discontinued the use of both shortly after receiving each of them because of adverse effects. Over a few weeks of follow-up, her symptoms have not improved. She still complains of postprandial abdominal discomfort, while her weight is now stable. Because of the unclear natural history of CG and no standard therapy regimens, we have decided to do follow-up esophagogastroduodenoscopies with a histological examination of corresponding specimens before starting a more aggressive therapeutic approach (e.g. steroids). We plan to do the first follow-up endoscopic investigation in about one year after the initial diagnosis. The lack of possible etiopathogenic factors remains the main problem, which disables us to start causal treatment (e.g. treatment of concurrent immune-related disorders, discontinuation of certain drugs). Our current conclusion is that the patient's symptoms and clinical findings are most likely multifactorial – a combination of the relapsing eating disorder, functional gastrointestinal disorder (irritable bowel syndrome), gastroparesis and CG. The correlation and causality between these entities, if any at all, is unclear and will be hard to prove. Multidisciplinary approach will be needed in the future to form a proper treatment strategy.

Discussion

Etiology and pathogenesis of CG is unknown, but autoimmune mechanisms, drugs and infection have been postulated as possible etiopathogenic factors.[2,4,5] CG has been described in patients with immune-related disorders, including celiac disease,[6,7] Sjögren syndrome,[8] systemic lupus erythematosus,[9] common variable immune deficiency (CVID),[10] lymphocytic gastritis, lymphocytic colitis and ulcerative colitis,[2] Hashimoto thyroiditis and polymyositis,[11] juvenile arthritis, rheumatoid arthritis, Graves disease and diabetes mellitus type 1.[12] Collectively, these associations support the hypothesis that collagenous gastroenteritides might be related to immune mechanisms.[13,14] A subset of CG cases may be attributed to drugs, such as olmesartan, an angiotensin II receptor blocker,[15] and venlaflaxine, an antidepressant.[12]

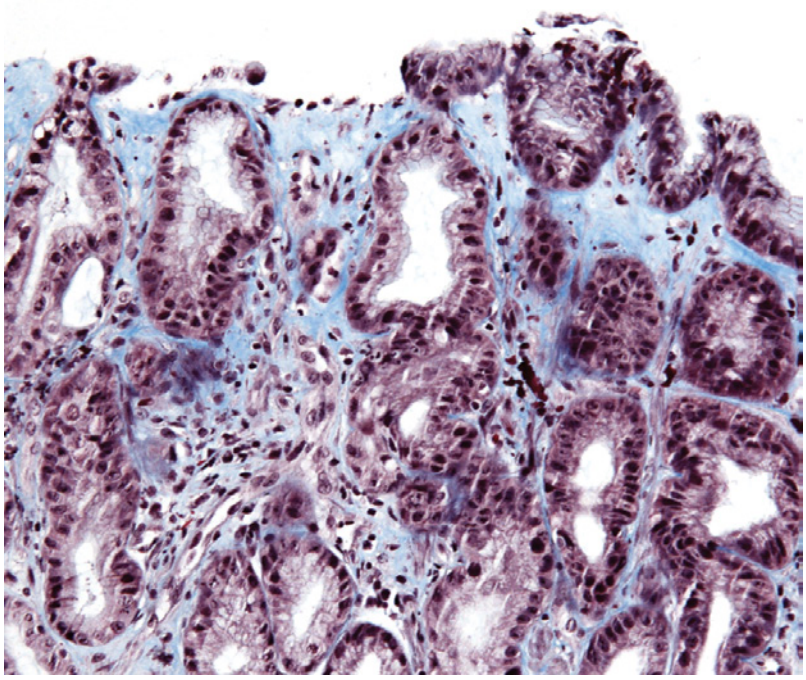

Figure 3: Blue staining of the subepithelial fibrous tissue by Masson's trichrome stain, orig. magn. 20x.

Patients of a wide age range present with epigastric and/or abdominal pain, anemia, gastrointestinal bleeding, diarrhea, nausea and vomiting, perforated ulcer, weight loss, abdominal distention, fatigue, dyspepsia, retrosternal pain, constipation and dysphagia.[1,12,16]. Previous studies have proposed two clinicopathologic types of CG on the basis of patient's age at disease onset:[6,8,11] (a) pediatric type (18 years of age or younger) presenting with severe anemia, nodular gastric mucosa and isolated gastric disease;[17] and (b) adult type with chronic watery diarrhea that is associated with diffuse collagenous involvement of the gastrointestinal tract.[6] However, notable exceptions exist and a broad variability in clinical presentation, etiology, treatment and disease course has been reported.[12] Within the most recent published papers, no statistically significant differences in clinical presentation or endoscopic findings among children and adults were seen.[7,12]

The characteristic endoscopic finding in CG is nodularity of the gastric corpus,[1,12,18] but it is not seen in all cases. Interestingly, the nodular lesions represent the undamaged mucosa, and the depressed areas surrounding the nodules are the result of inflammation with atrophic changes and collagen deposition.[18] The other endoscopic findings include mucosal erythema, erosions and exudate.[1,12]

The diagnosis of CG is made by histology – in order to make a diagnosis it is necessary to take biopsy specimens according to the updated Sydney protocol: two specimens from the antrum, two specimens from the corpus and one specimen from the incisura angularis. Especially in the early stages, the disease can be unevenly distributed over the gastric mucosa, thus it is important to take at least five specimens. Furthermore, additional biopsy samples must be taken from any macroscopically unusual regions. Histology shows distinctive findings: infiltration of chronic inflammatory cells in the lamina propria, and the deposition of collagen bands thicker than 10 μm.[2,19] The inflammatory cells include lymphocytes, plasma cells, and eosinophils. A recent study[7] identified 3 distinct histological patterns of collagenous gastritis: (a) an eosinophil-rich pattern (more than 30 lamina propria eosinophils per high-power field), (b) a lymphocytic gastritis-like pattern (at least 25 intraepithelial lymphocytes per 100 surface epithelial cells) and (c) an atrophic pattern (involves the gastric corpus with marked loss of the oxyntic glands, pyloric metaplasia and minimal ECL cell hyperplasia).[12] Clinically, the lymphocytic gastritis-like pattern is believed to be associated with celiac disease, collagenous sprue, and/or collagenous colitis.[7]

CG, collagenous colitis and collagenous sprue are thought to be part of the same disease entity – collagenous gastroenteritides. Especially in adult type

of CG, it is important to rule out the possible concurrent collagenous sprue or collagenous colitis, which can be done by histological examination of the duodenal biopsies and colon biopsies obtained during esophagogastroduodenoscopy and colonoscopy, respectively. Both were done in our patient and the histologic changes were not diagnostic for collagenous sprue or collagenous colitis.

Inflammation causes gland atrophy and leads to the depressed mucosal pattern found on endoscopy.[18] The diagnostic pathological features are less marked in the nodular lesions.[18] Several mucosal biopsies are therefore needed for correct diagnosis and careful mapping is required for the follow-up of mucosal inflammation and the thickness of collagen deposits.[1] Collagen deposition can be visualized with Masson trichrome staining and tenascin immunohistochemistry.[7] Collagen analysis has been performed in a few patients with CG and revealed the presence of collagen types III and VI.[6,20-23] Type III collagen is released by subepithelial fibroblasts to repair damage caused by inflammation. Therefore, collagen synthesis in CG is probably a reparative response.[20] The thickness of the collagen deposits may increase with disease duration; however, it may also be influenced by the location of the biopsy rather than the severity of the disease.[2,6,11,24,25]

Because of the small number of cases and the unknown etiology, no standard therapy has been established. Anti-secretory agents including proton pump inhibitors,[4,9,11,17,19-22,25-32] and H2--receptor antagonists,[3,20,21,31,32] steroids,[2,6,11,16,19,23,25,27,29,33] iron supplementation[14,17,19,20,24-26,34] and hypoallergenic diets[8,11,20] have been tried with limited success. Other treatment modalities, such as sucralfate,[3,11,21,27] mesalazine,[2,19,29] bismuth subsalicylate,[29] furazolidone,[3] sulfasalazine,[6,35] azathioprine,[16] and parenteral nutrition[6,16,33] have also been tested. A few patients have shown improvement of the clinical symptoms but no randomized, controlled trials have been performed.[1] In addition, the lack of symptoms does not necessarily correlate with the negative follow-up biopsies or *vice versa*.[12] Also, the eradication of *Helicobacter pylori* did not produce any therapeutic benefit.[1] Further cases are needed to establish a standard therapeutic strategy.

The natural history of CG is also unclear. Although regarded by many investigators as a chronic but benign disorder, a 12-year follow up study of the first patient diagnosed with CG revealed progressive glandular atrophy, intestinal metaplasia, linear neuroendocrine hyperplasia and surface epithelial changes interpreted as indefinite for dysplasia.[21] This raises the possibility that CG may be a predisposing factor for gastric neuroendocrine tumors and adenocarcinoma. Although the course of CG remains uncertain, none of the patients described in the recent studies developed dysplasia and/or invasive adenocarcinoma.[7,12] Moreover, there are known cases of CG which showed complete absence of collagen deposits,[6,17] improvement of inflammation,[6] or a moderate decrease in the thickness of subepithelial collagen deposits[17] on biopsies obtained a few years after the initial diagnosis. Patients who recovered had been treated with: (a) steroid, sulfasalazine, and parenteral alimentation;[6] (b) oral iron supplementation and proton-pump inhibitors.[17] However, in most cases, the collagen deposits remain unchanged or become thicker as a result of continued inflammation.[1]

There are number of potential pitfalls in diagnosing CG. Considering the rarity of this condition with respect to collagenous deposition at other gastrointe-

stinal sites, CG may be underdiagnosed. Indeed, reassessment of prior biopsies in a recent study showed misdiagnosed or overlooked cases of CG.[12] In these cases, a prominent subepithelial collagen layer was overlooked, but associated symptoms, such as diarrhea and anemia, and gastric nodularity on endoscopy were present.[12] Although CG is a histological diagnosis, the combination of other key clinical and endoscopic findings should prompt consideration of this entity. The other problem that can lead to misdiagnosis is the fact that collagen deposition within the lamina propria can be seen in other conditions, such as ischemia and radiation-induced injury. However, in these cases the distribution of collagen is typically diffuse rather than subepithelial.[36] Moreover, fibrin in the setting of an erosion or amyloid deposits around blood vessels may be misdiagnosed as CG.[12] Additional stains for collagen, such as Masson trichrome or immunohistochemistry for tenascin, are of great use in these situations.

Conclusion

Collagenous gastritis is a rare and diagnostically challenging disease. Gastroenterologists and pathologists need to be aware of this condition, otherwise it can be easily overlooked. Even though CG is a histological diagnosis, the combination of clinical and endoscopic findings should prompt consideration of this entity. No safe and effective treatments have been identified. Therefore, better understanding of the disease and analysis of larger number of patients is needed to establish diagnostic criteria and to develop therapeutic strategies.

Literature

1. Kamimura K, Kobayashi M, Sato Y, Aoyagi Y, Terai S. Collagenous gastritis: Review. World J Gastrointest Endosc 2015; 7: 265–73.
2. Vesoulis Z, Lozanski G, Ravichandran P, Esber E. Collagenous gastritis: a case report, morphologic evaluation, and review. Mod Pathol 2000; 13: 591–6.
3. Colletti RB, Trainer TD. Collagenous gastritis. Gastroenterology 1989; 97: 1552–5.
4. Kori M, Cohen S, Levine A, Givony S, Sokolovskaia-Ziv N, Melzer E, et al. Collagenous gastritis: a rare cause of abdominal pain and iron-deficiency anemia. J Pediatr Gastroenterol Nutr 2007; 45: 603–6.
5. Jain R, Chetty R. Collagenous gastritis. Int J Surg Pathol 2010; 18: 534–6.
6. Lagorce-Pages C, Fabiani B, Bouvier R, Scoazec JY, Durand L, Flejou JF. Collagenous gastritis: a report of six cases. Am J Surg Pathol 2001; 25: 1174–9.
7. Arnason T, Brown IS, Goldsmith JD, Anderson W, O'Brien BH, Wilson C, et al. Collagenous gastritis: a morphologic and immunohistochemical study of 40 patients. Mod Pathol 2015; 28: 533–44.
8. Stancu M, De Petris G, Palumbo TP, Lev R. Collagenous gastritis associated with lymphocytic gastritis and celiac disease. Arch Pathol Lab Med 2001; 125: 1579–84.
9. Al-Kandari A, Al-Alardati H, Sayadi H, Al-Judaibi B, Mawardi M. An unusual case of collagenous gastritis in a middle- aged woman with systemic lupus erythromatosis: a case report. J Med Case Rep 2014; 8: 278.
10. Daniels JA, Lederman HM, Maitra A, Montgomery EA. Gastrointestinal tract pathology in patients with common variable immunodeficiency (CVID): a clinicopathologic study and review. Am J Surg Pathol 2007; 31: 1800–12.
11. Leung ST, Chandan VS, Murray JA, Wu TT. Collagenous gastritis: histopathologic features and association with other gastrointestinal diseases. Am J Surg Pathol 2009; 33: 788–98.
12. Ma C, Park JY, Montgomery EA, Arnold CA, McDonald OG, Liu TC, et al. A Comparative Clinicopathologic Study of Collagenous Gastritis in Children and Adults: The Same Disorder With Associated Immune-mediated Diseases. Am J Surg Pathol 2015; 39: 802–12.
13. Gillett HR, Freeman HJ. Prevalence of celiac disease in collagenous and lymphocytic colitis. Can J Gastroenterol 2000; 14: 919–21.
14. Park S, Kim DH, Choe YH, Suh YL. Collagenous gastritis in a Korean child: a case report. J Korean Med Sci 2005; 20: 146–9.
15. Rubio-Tapia A, Herman ML, Ludvigsson JF, Kelly DG, Mangan TF, Wu TT, et al. Severe spruelike enteropathy associated with olmesartan. Mayo Clin Proc 2012; 87: 732–8.
16. Wang HL, Shah AG, Yerian LM, Cohen RD, Hart J. Collagenous gastritis: an unusual association with profound weight loss. Arch Pathol Lab Med 2004; 128: 229–32.

17. Hijaz NM, Septer SS, Degaetano J, Attard TM. Clinical outcome of pediatric collagenous gastritis: case series and review of literature. World J Gastroenterol 2013; 19: 1478–84.
18. Kamimura K, Kobayashi M, Narisawa R, Watanabe H, Sato Y, Honma T, et al. Collagenous gastritis: endoscopic and pathologic evaluation of the nodularity of gastric mucosa. Dig Dis Sci 2007; 52: 995–1000.
19. Suskind D, Wahbeh G, Murray K, Christie D, Kapur RP. Collagenous gastritis, a new spectrum of disease in pediatric patients: two case reports. Cases J 2009; 2: 7511.
20. Brain O, Rajaguru C, Warren B, Booth J, Travis S. Collagenous gastritis: reports and systematic review. Eur J Gastroenterol Hepatol 2009; 21: 1419–24.
21. Winslow JL, Trainer TD, Colletti RB. Collagenous gastritis: a long-term follow-up with the development of endocrine cell hyperplasia, intestinal metaplasia, and epithelial changes indeterminate for dysplasia. Am J Clin Pathol 2001; 116: 753–8.
22. Kajino Y, Kushima R, Koyama S, Fujiyama Y, Okabe H. Collagenous gastritis in a young Japanese woman. Pathol Int 2003; 53: 174–8.
23. Castellano VM, Muñoz MT, Colina F, Nevado M, Casis B, Solís-Herruzo JA. Collagenous gastrobulbitis and collagenous colitis. Case report and review of the literature. Scand J Gastroenterol 1999; 34: 632–8.
24. Wilson C, Thompson K, Hunter C. Nodular collagenous gastritis. J Pediatr Gastroenterol Nutr 2009; 49: 157.
25. Dray X, Reignier S, Vahedi K, Lavergne-Slove A, Marteau P. Collagenous gastritis. Endoscopy 2007; 39 Suppl 1: E292–3.
26. Rustagi T, Rai M, Scholes JV. Collagenous gastroduodenitis. J Clin Gastroenterol 2011; 45: 794–9.
27. Côté JF, Hankard GF, Faure C, Mougenot JF, Holvoet L, Cézard JP, et al. Collagenous gastritis revealed by severe anemia in a child. Hum Pathol 1998; 29: 883–6.
28. Freeman HJ. Topographic mapping of collagenous gastritis. Can J Gastroenterol 2001; 15: 475–8.
29. Leiby A, Khan S, Corao D. Clinical challenges and images in GI. Collagenous gastroduodenocolitis. Gastroenterology 2008; 135: 17, 327.
30. Jin X, Koike T, Chiba T, Kondo Y, Ara N, Uno K, et al. Collagenous gastritis. Dig Endosc 2013; 25: 547–9.
31. Tanabe J, Yasumaru M, Tsujimoto M, Iijima H, Hiyama S, Nishio A, et al. A case of collagenous gastritis resembling nodular gastritis in endoscopic appearance. Clin J Gastroenterol 2013; 6: 442–6.
32. Soeda A, Mamiya T, Hiroshima Y, Sugiyama H, Shidara S, Dai Y, et al. Collagenous gastroduodenitis coexisting repeated Dieulafoy ulcer: A case report and review of collagenous gastritis and gastroduodenitis without colonic involvement. Clin J Gastroenterol 2014; 7: 402–9.
33. Billiémaz K, Robles-Medranda C, Le Gall C, Gay C, Mory O, Clémenson A, et al. A first report of collagenous gastritis, sprue, and colitis in a 9-month-old infant: 14 years of clinical, endoscopic, and histologic follow-up. Endoscopy 2009; 41 Suppl 2: S233–4.
34. Ravikumara M, Ramani P, Spray CH. Collagenous gastritis: a case report and review. Eur J Pediatr 2007; 166: 769–73.
35. Groisman GM, Meyers S, Harpaz N. Collagenous gastritis associated with lymphocytic colitis. J Clin Gastroenterol 1996; 22: 134–7.
36. Crowder CD, Grabowski C, Inampudi S, Sielaff T, Sherman CA, Batts KP. Selective internal radiation therapy-induced extrahepatic injury: an emerging cause of iatrogenic organ damage. Am J Surg Pathol 2009; 33: 963–75.