Clinical Case Report

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Three case reports of collagenous gastritis in children

Lessons for an endoscopic and histologic approach to mucosal nodularity of the stomach

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Abstract

Rationale: Collagenous gastritis (CG) is a rare form of chronic gastritis defined histologically by a thickened subepithelial collageneous band in the lamina propria. However, the clinical features and endoscopic findings of CG have not been clearly established in the pediatric population.

Presenting concerns: We report the cases of 3 children who presented with intractable anemia and minimal or no gastrointestinal (GI) symptoms and were followed up without definitive diagnosis determination even through diagnostic endoscopic evaluations.

Diagnoses: On repeated endoscopic examination, we determined thickened subepithelial collagen band, confirmed by Masson trichrome staining using targeted biopsies of the intervening mucosa between the prominent nodular lesions.

Interventions: Under the diagnosis of CG, a course of steroid was administrated in 1 patient, while all patients continued oral iron replacement therapy.

Outcomes: All 3 patients remained asymptomatic and their anemia was alleviated with continued administration of oral iron.

Main lessons: We recommend early endoscopic evaluation for patients with unexplained anemia, emphasizing a high index of suspicion for CG, despite the absence of definitive GI symptoms. Targeted gastric biopsies should be performed in the depressed mucosa surrounding the nodules, as well as the nodules themselves, to confirm CG, when presented with nodular gastric mucosa in endoscopy.

Abbreviations: CG = collagenous gastritis, EGD = esophagogastroduodenoscopy, GI = gastrointestinal, Hb = hemoglobin, IDA = iron deficiency anemia, MCV = mean corpuscular volume, NG = nodular gastritis, OB = occult blood, PPI = proton pump inhibitor, TIBC = total iron binding capacity, WBC = white blood cell.

Keywords: anemia, case series, child, collagen, endoscopy, gastritis

1. Introduction

Collagenous gastritis (CG) is a rare and unusual form of gastritis, with only about 60 cases reported worldwide to date.[1] The diagnosis of CG is based on histological features of subepithelial collagen deposition with inflammatory cell infiltration of the lamina propria.[2] Two clinical phenotypes have been described for adult and pediatric-onset diseases.[1–3] However, the typical clinical manifestations that suggest CG and require endoscopy for confirmation have not been clearly determined.[1] In addition, there do not seem to be any characteristic endoscopic findings that are specific to CG, although there have been several reports describing grossly abnormal endoscopic features in children with CG.[1,4] Therefore, CG is a diagnostically challenging entity for gastrointestinal (GI) endoscopists as well as general pediatricians.

We describe 3 cases of pediatric CG with complicated diagnoses. Through these case studies, we aim to provide insight into endoscopic and pathologic considerations for early diagnosis of CG in children.

2. Case report

2.1. Patient 1

An 8-year-old boy presented with a 6-month history of intermittent vomiting, which occurred only once or twice per month. He did not complain of dysphagia, abdominal pain, diarrhea, or melena. Physical examination was unremarkable, with a body weight in the 15–25th percentile and height in the 50–75th percentile. Initial laboratory tests showed a hemoglobin

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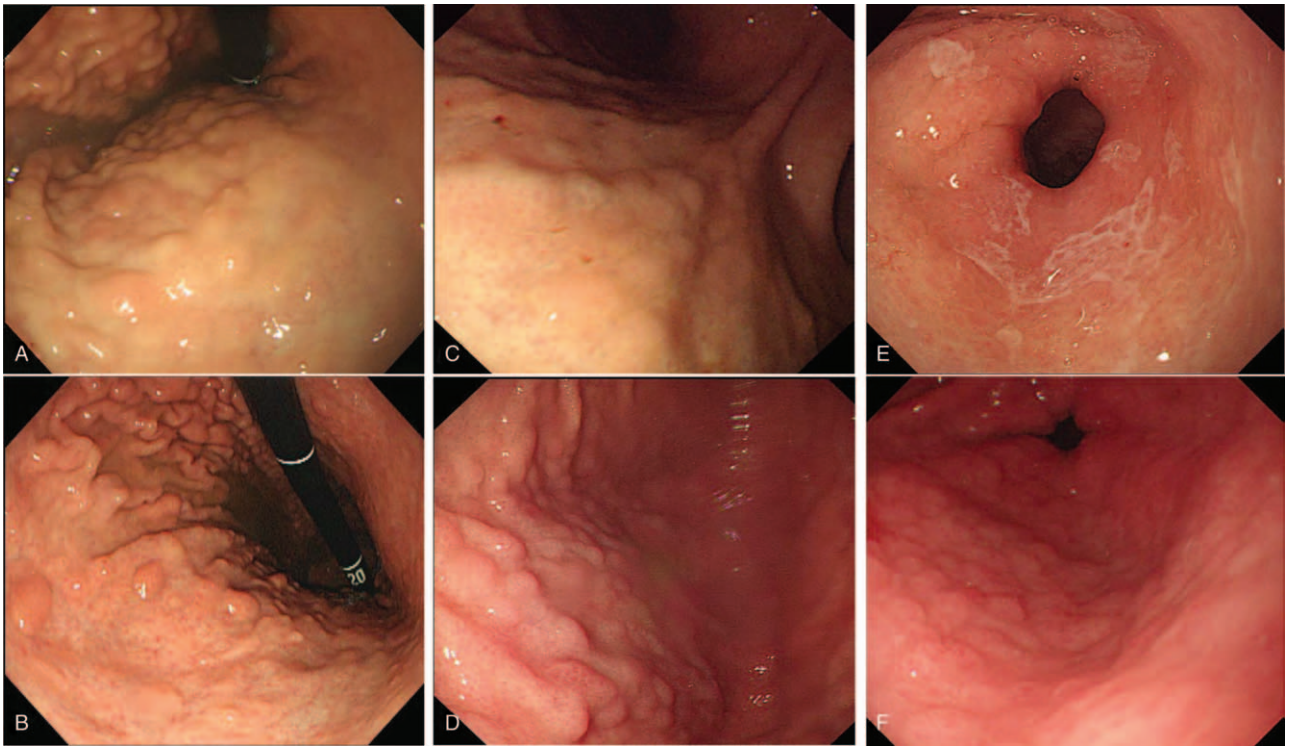

Figure 1. Esophagogastroduodenoscopic findings of the 3 patients. A, Initial endoscopy of patient 1 revealed diffusely nodular mucosa in the gastric body. B, The 6-month follow-up endoscopy of patient 1 demonstrated more prominent nodularity and multiple polypoid lesions with pale background mucosa. C, Initial endoscopy of patient 2 revealed coarsely nodular mucosa interspersed in the gastric body. D, The 20-month follow-up endoscopy of patient 2 demonstrated a striking nodularity of the gastric body. E, Initial endoscopy of patient 3 revealed edematous mucosa and multiple ulcerations with whitish mucus throughout the gastric antrum. F, The 7-month follow-up endoscopy of patient 3 demonstrated prominent nodularity on the gastric antrum.

(Hb) level of 10.4 g/dL, a white blood cell (WBC) count of 5800/mm^3, mean corpuscular volume (MCV) of 80 fl, ferritin level of 3.5 ng/mL, iron level of 25 μg/dL, and total iron binding capacity (TIBC) of 390 μg/dL. Serum inflammatory markers (erythrocyte sedimentation rate and C-reactive protein) were normal. Occult blood (OB) in the stool was absent. Iron replacement therapy (5 mg/kg/d) was initiated combined with an initial 2-week course of histamine receptor antagonist. Over the next 6 months, his vomiting ceased and his iron status showed slight improvement.

About 1 year thereafter, he presented again with an increased frequency of vomiting without associated diarrhea or abdominal pain. Laboratory tests revealed that his iron status had worsened: he had a Hb level of 8.6 g/dL, MCV of 65 fl, ferritin of 2.4 ng/mL, iron level of 19 μg/dL, and TIBC of 414 μg/dL. Stool OB was positive. Esophagogastroduodenoscopy (EGD) revealed nodular mucosa throughout the gastric body with relative sparing of the antrum (Fig. 1A). Biopsies from the nodules showed chronic active gastritis, consisting of lymphocytes and eosinophils with no detected *Helicobacter pylori* organisms or granulomas. The colonoscopy with biopsy was unremarkable.

The patient was treated with a proton pump inhibitor (PPI) and iron supplementation during follow-up. His Hb level returned to normal, but his ferritin levels were consistently low. A second EGD, performed after an interval of 6 months, showed more prominent nodular mucosa in the gastric body. The nodules were well demarcated and more irregular in size, with multiple small polypoid lesions (Fig. 1B). Biopsies performed in the intervening mucosa between the polypoid lesions revealed patchy deposition of collagenous tissue with prominent eosinophil infiltration in the lamina propria (Fig. 2A, D). These findings were not observed in the first biopsy specimens. Once the diagnosis of CG was confirmed, a 10-week course of prednisolone with a PPI was administered for his newly developed symptom of abdominal pain and his intractable vomiting. On the 6-month follow-up, his clinical symptoms improved and his iron level was within the normal range with continued iron supplementation.

2.2. Patient 2

An 11-year-old boy was referred to the GI clinic for the evaluation of intractable anemia. He had previously been diagnosed with iron deficiency anemia (IDA) and had been treated with the usual dose of oral iron supplements in our hematology department. He complained of fatigue but did not have any GI symptoms. On examination, he was pale, with a body weight in the 25–50th percentile and height in the 90–97th percentile. His initial laboratory evaluation revealed a Hb level of 6.0 g/dL, WBC count of 6480/mm^3, MCV of 60 fl, ferritin level of < 5 ng/mL, iron level of 15 μg/dL, and TIBC of 472 μg/dL. EGD revealed coarsely nodular mucosa in the gastric body with antrum having a normal appearance (Fig. 1C). Histologic examination showed diffuse lymphocytic infiltrations with no *H pylori* or lymphoid follicles, and the histologic diagnosis was chronic active gastritis. Ileocolonoscopy with colon biopsy and capsule endoscopy were unremarkable.

Since no focus of GI bleeding was identified, he was treated with oral iron replacement during follow-up. His Hb levels, which reached a maximum of 11.4 g/dL, were dependent on iron intake and fluctuated with changes in his adherence to treatment. Follow-up EGD, at an interval of 20 months, showed striking

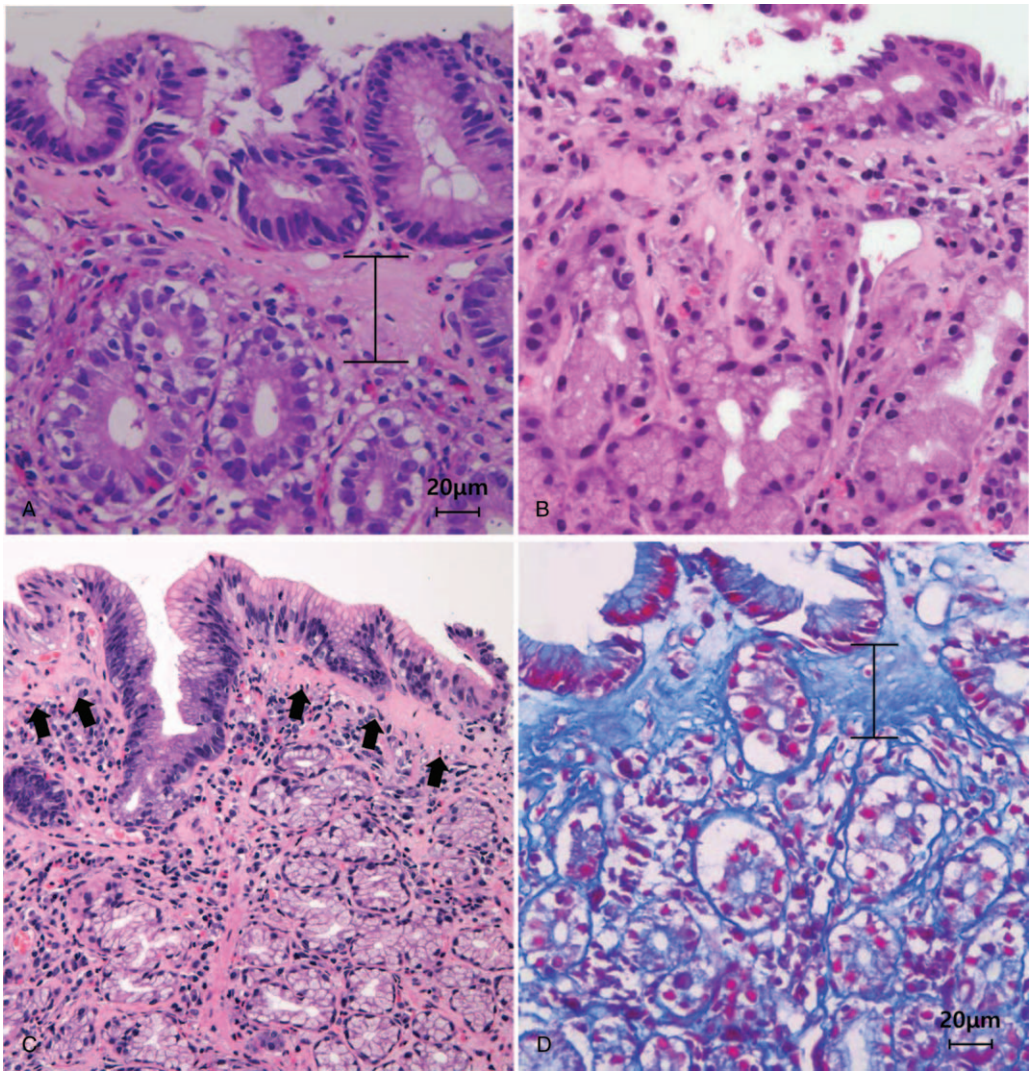

Figure 2. Histopathologic examinations of the biopsy specimens. A, Biopsy taken from the intervening mucosa between polypoid lesions of patient 1 showed patchy deposition of collagenous tissue in the lamina propria, where the thickness was maximally 50.6 μm and eosinophilic infiltration is prominent (40–70 eosinophils/high power field, hematoxylin and eosin (H&E), ×400 magnification). B, A follow-up endoscopy with biopsy of patient 2 revealed focally fibrocollagenous deposition in the lamina propria with partial damage and detachment of the surface epithelium (H&E, ×400 magnification). C, A follow-up endoscopy with biopsy of patient 3 showed a subepithelial collagen band averaging 35 to 45 μm thickness with mild inflammation (H&E, ×200 magnification). D, Corresponding Masson Trichrome stain of the tissue of patient 1 showed a blue thick band of collagen in the subepithelial area measuring up to 43.8 μm in thickness (×400 magnification).

nodularity of the gastric body with relative sparing of the antrum (Fig. 1D). Repeat histology demonstrated focal deposition of fibrocollagenous tissue and a diffuse lymphoplasmacytic infiltrate in the lamina propria, with partial detachment of the surface epithelium, consistent with CG (Fig. 2B). Once the diagnosis of CG was confirmed, he was continued on oral iron and has had regular follow-up. He has remained asymptomatic with normal growth and resolution of his anemia.

2.3. Patient 3

A 15-year-old asymptomatic girl was referred for a further opinion regarding possible occult GI bleeding. Prior to her referral, she has been diagnosed with IDA, with recurrent episodes requiring oral or intravenous iron over the 4 years. She denied any medication. Menstruation was normal. Her initial Hb level was 8.1 g/dL, reaching a maximum of 14.8 g/dL with treatment, but decreasing to 10.5 g/dL after discontinuation of iron therapy. Physical examination and other laboratory tests were unremarkable, and growth was normal.

EGD with multiple biopsies revealed edematous mucosa and multiple ulcerations with whitish mucus throughout the gastric antrum, histologically chronic active gastritis without identification of *H pylori,* cytomegalovirus or granuloma (Fig. 1E). Ileocolonoscopy and capsule endoscopy findings were unremarkable. Although there was no evidence of occult GI blood loss, her anemia did not completely resolve with continuation of oral iron supplementation and short course of a PPI. Follow-up EGD 7 months later revealed prominent nodularity in the antrum (Fig. 1F) and a few polyps on the gastric body (not seen in the figure). Multiple biopsies from the intervening mucosa between polyps showed an irregular subepithelial collagenous band averaging 35 to 45 μm thickness, which confirmed the diagnosis of CG. She has been doing well without GI symptoms and has maintained hemoglobin levels of over 12 g/dL with continuing oral iron supplementation.

3. Discussion

We describe the clinical course of 3 children with CG over several years who presented with intractable anemia and minimal or no GI symptoms. They all had to undergo at least 2 endoscopic examinations and repeated biopsies to confirm the definitive diagnosis of CG. The characteristic collagen deposition, which was histochemically confirmed by Masson trichrome staining, could be detected only in tissue specimens obtained through targeted biopsies of the intervening mucosa between nodules, and not of the nodules themselves.

Gastric mucosal nodularity is frequently seen in the general practice of endoscopic procedures. It is indicative of inflammatory cell infiltration and lymphoid hyperplasia in the stomach, and is often described as nodular gastritis (NG), even though there is no established endoscopic definition of NG.[5] NG has also been called antral nodularity, nodular antritis, gastric lymphoid hyperplasia, follicular gastritis, or lymphofollicular gastritis, which are more common in the gastric antrum.[6] NG is frequently associated with *H pylori* infection, mainly in children.[7] In addition, NG may be observed in mucosa-associated lymphoid tissue lymphoma or gastric cancer.[8] Therefore, one should differentiate between underlying diseases, which may present with similar appearance, when a gastric nodular pattern is encountered on endoscopy.

Endoscopic findings of CG are reported to vary depending on age, from normal mucosa to diffuse gastric erythema, erosions, gastric hemorrhages, nodular mucosa, and polypoid lesions.[1,4] Mucosal nodularity is considered the most characteristic findings of CG in children and young adults.[4] In comparison with other underlying diseases of NG, wherein the nodules are uniform in size and mainly found in the antrum, the nodules in the cases described here were more irregular and prominently occurred in the gastric body rather than the antrum. On follow-up endoscopy, the nodules had become well demarcated, and the mucosa had a polypoid-protruding rather than miliary nodular or granular pattern. A previous Japanese study has reported cases presenting with pseudopolyposis or cobblestone-like mucosa confined to the gastric body; 1 case showed a change from nodular to polypoid mucosa over 4 years, as seen in our case.[9,10]

Histologically, the nodules in NG are aggregations of lymphoid follicles or an involvement of malignant cells.[6] Meanwhile, the nodules of CG are caused not by swelling of the mucosa due to inflammation, but by depression of the inflamed mucosa surrounding the nodules.[11] The nodular mucosa in CG shows fewer inflammatory infiltrates with preserved normal architecture, while the surrounding mucosa shows remarkable inflammatory infiltrates and damaged glandular structure with a thickened subepithelial collagen band. These changes lead to atrophy and a depressed mucosa; these areas should be targeted when performing endoscopic biopsy to confirm a diagnosis of CG.[10,11] The uneven and irregular inflammatory process in the mucosa causes the nodular or polypoid change, although the reason for the heterogeneity of the degree of the inflammation remains unknown.[1,11] In fact, the polypoid mucosal changes in our cases during the follow-up endoscopies at the interval of 6 to 20 months reflect the progression of the inflammation over time.

During the first endoscopic biopsies, the intervening depressed lesions between the less prominent nodules were too narrow in width to target for biopsy, resulting in failure to detect the collagen deposition. However, on our follow-up endoscopies, more prominent nodular mucosa and polypoid changes made it possible to target and obtain tissue from the intervening mucosa around the nodules and pseudopolyps, finally allowing detection of the thickened collagenous band in the lamina propria and confirming CG. In addition, we were able to exclude the possibility of *H plyori* infection, cytomegalovirus infection or malignancy through multiple biopsies. Based on our experience, we recommend taking a targeted biopsy of the depressed intervening mucosa surrounding the nodules, as well as the nodular lesions, which many practitioners consider the pathologic lesions. In addition, careful mapping during the biopsy procedure is required for a definitive diagnosis and follow-up of the inflammation.

There have been about 20 pediatric case reports of CG worldwide since the first case of 15-year-old girl was reported in 1989.[12] The literatures divide CG into 2 subsets of pediatric-onset and adult-onset disease.[1–3] Pediatric-onset CG is reported to be related to inflammatory changes limited to the stomach, while adult-onset CG often involves other parts of the GI tract that are associated with collagenous colitis or collagenous sprue. Based on a recent pediatric case review, the 2 phenotypes are suggested to be part of a continuous disease spectrum.[4] However, the children in the present report did not present with adult phenotypes, such as voluminous diarrhea, during the follow-up period of several years. Among our 3 patients, only 1 patient displayed the GI symptom of vomiting, which happened infrequently when he was forced to eat food that he did not like. We first suspected the boy to have uncomplicated reflux, since he did not show any alarming signs such as growth failure, and his vomiting subsided with short-term acid suppression therapy. Meanwhile, all patients presented with a long-term history of iron replacement for IDA without definitive symptoms and signs of GI bleeding. Therefore, we recommend early endoscopy for poor response to the usual dose of iron supplementation, even in the absence of definitive GI symptoms.

Since the etiology of CG is unknown, there is no established standard therapy, although several treatment modalities have been suggested.[1,4] In addition, the long-term outcome and prognosis are still poorly documented.[13] In our series, the patient who developed abdominal pain achieved clinical improvement after administration of corticosteroid for 10 weeks. However, he still required iron supplementation to control his anemia. The etiology of anemia in CG has been considered to be blood loss associated with mucosal tissue abrasion and damage of dilated capillaries entrapped in the subepithelial collagen band, rather than intestinal malabsorption of iron.[4,14] In children with CG, who have a chronic and indolent clinical course, iron replacement will be needed long-term, regardless of the mucosal condition on endoscopy.[13] Based on our experience, it seems unclear whether long-term acid suppression is necessary for the treatment of anemia in patients with CG without other GI symptoms.

4. Conclusion

Although CG is very rare in children, we recommend early endoscopic evaluation with tissue biopsy to confirm CG in patients with unexplained anemia; a high index of suspicion for CG should be maintained despite the absence of definitive GI symptoms. In addition, targeted gastric biopsies should be performed in the depressed mucosa surrounding the nodules, as well as the nodules themselves, to establish the presence of collagen deposition when presented with nodular gastric mucosa found on endoscopy.

This case series was approved by the institutional review board (IRB) of Pusan National University Yangsan Hospital (IRB No.

05-2018-184) and the requirement for informed consents was waived due to the retrospectively collected data. The patients and their parents were informed, and they provided their permission for their data to be included in the manuscript with assured anonymity of the patients

Author contributions

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References

[1] Kamimura K, Kobayashi M, Sato Y, et al. Collagenous gastritis: review. World J Gastrointest Endosc 2015;7:265–73.
[2] Brain O, Rajaguru C, Warren B, et al. Collagenous gastritis: reports and systematic review. Eur J Gastroenterol Hepatol 2009;21:1419–24.
[3] Lagorce-Pages C, Fabiani B, Bouvier R, et al. Collagenous gastritis: a report of six cases. Am J Surg Pathol 2001;25:1174–9.
[4] Matta J, Alex G, Cameron DJS, et al. Pediatric collagenous gastritis and colitis: a case series and review of the literature. J Pediatr Gastroenterol Nutr 2018;67:328–34.
[5] Genta RM, Hamner HW, Graham DY. Gastric lymphoid follicles in Helicobacter pylori infection: frequency, distribution, and response to triple therapy. Hum Pathol 1993;24:577–83.
[6] Miyamoto M, Haruma K, Yoshihara M, et al. Nodular gastritis in adults is caused by Helicobacter pylori infection. Dig Dis Sci 2003; 48:968–75.
[7] Bahu Mda G, da Silveira TR, Maguilnick I, et al. Endoscopic nodular gastritis: an endoscopic indicator of high-grade bacterial colonization and severe gastritis in children with Helicobacter pylori. J Pediatr Gastroenterol Nutr 2003;36:217–22.
[8] Kamada T, Tanaka A, Yamanaka Y, et al. Nodular gastritis with Helicobacter pylori infection is strongly associated with diffuse-type gastric cancer in young patients. Dig Endosc 2007;19:180–4.
[9] Jin X, Koike T, Chiba T, et al. Collagenous gastritis. Dig Endosc 2013;25:547–9.
[10] Tanabe J, Yasumaru M, Tsujimoto M, et al. A case of collagenous gastritis resembling nodular gastritis in endoscopic appearance. Clin J Gastroenterol 2013;6:442–6.
[11] Kamimura K, Kobayashi M, Narisawa R, et al. Collagenous gastritis: endoscopic and pathologic evaluation of the nodularity of gastric mucosa. Dig Dis Sci 2007;52:995–1000.
[12] Colletti RB, Trainer TD. Collagenous gastritis. Gastroenterology 1989; 97:1552–5.
[13] Hijaz NM, Septer SS, Degaetano J, et al. Clinical outcome of pediatric collagenous gastritis: case series and review of literature. World J Gastroenterol 2013;19:1478–84.
[14] Cote JF, Hankard GF, Faure C, et al. Collagenous gastritis revealed by severe anemia in a child. Hum Pathol 1998;29:883–6.