Acta Med. Okayama, 2023
Vol. 77, No. 1, pp. 75–80

Acta Medica Okayama
http://escholarship.lib.okayama-u.ac.jp/amo/

Case Report

Scattered Tiny Whitish Protrusions in the Stomach Are a Clue to the Diagnosis of Autoimmune Gastritis

Masaya Iwamuro[a]*, Takehiro Tanaka[b], Kenta Hamada[a], Yoshiyasu Kono[a], Hiromitsu Kanzaki[a], Seiji Kawano[a], Yoshiro Kawahara[c], and Hiroyuki Okada[a]

[a]*Departments of Gastroenterology and Hepatology,*
[b]*Pathology, Okayama University Graduate School of Medicine, Dentistry and Pharmaceutical Sciences,*
[c]*Department of Practical Gastrointestinal Endoscopy, Okayama University Hospital, Okayama 700-8558, Japan*

Herein, we report two patients with autoimmune gastritis who had undergone multiple esophagogastroduodenoscopy procedures for 17 and 9 years, respectively, before their diagnosis. Instead, they had been diagnosed with and treated for *Helicobacter pylori*-associated gastritis. The correct diagnosis was made when scatterings of tiny whitish protrusions in the gastric mucosa were detected on esophagogastroduodenoscopy. Our findings suggest that scattered tiny whitish bumps may be a clue to the diagnosis of autoimmune gastritis.

Key words: autoimmune gastritis, esophagogastroduodenoscopy, scattered lesions, small white protrusions, mucosal lesions

Autoimmune gastritis is an immune-mediated chronic inflammatory disease that causes destruction of the parietal cells of the stomach, thereby resulting in gastric mucosal atrophy [1-5]. Pernicious anemia is caused by vitamin B12 deficiency due to the loss of intrinsic factors, known as a clinical manifestations in patients with autoimmune gastritis because intrinsic factors are produced by parietal cells and are required for the uptake of vitamin B12. Severe or prolonged vitamin B12 deficiency may cause permanent nerve cell damage. Otherwise, vitamin B12 deficiency can be reversed by replacement therapy, involving the injection or peroral administration of vitamin B12. Thus, early intervention is required before vitamin B12 deficiency progresses [6-8]. It has also been reported that gastric neoplasms such as neuroendocrine tumors and adenocarcinomas can occur in the stomachs of patients with autoimmune gastritis [6]. In addition, patients with autoimmune gastritis are more likely to have iron-deficiency anemia and other autoimmune diseases, such as thyroid diseases, which are the most common of the autoimmune diseases [6,7,9]. Thus, prompt diagnosis followed by surveillance of related diseases and treatment is essential in those with autoimmune gastritis.

In patients with *Helicobacter pylori* infection, inflammation and mucosal atrophy progress from the gastric antrum in the proximal direction along the lesser curvature [10]. In contrast, the gastric fundus and corpus are more commonly affected by autoimmune gastritis [6,8,11]. Differentiation between *H. pylori*-associated and autoimmune gastritis can generally be performed via esophagogastroduodenoscopy based on the predominant sites of mucosal atrophy. However, patients with autoimmune gastritis often have concurrent *H. pylori* infections [12]. In such cases, the diagnosis of *H. pylori*-associated gastritis may delay the endoscopic discovery of autoimmune gastritis.

Herein, we report the cases of two patients with autoimmune gastritis. They were initially diagnosed

Received May 6, 2022; accepted August 8, 2022.
*Corresponding author. Phone: +81-86-235-7218; Fax: +81-86-225-5991
E-mail: iwamuromasaya@yahoo.co.jp (M. Iwamuro)

Conflict of Interest Disclosures: No potential conflict of interest relevant to this article was reported.

with *H. pylori*-associated gastritis. They each had undergone multiple esophagogastroduodenoscopies for 17 and 9 years, respectively. However, the correct diagnosis, autoimmune gastritis, was overlooked and was not made until the presence of scattered tiny whitish bumps on esophagogastroduodenoscopy prompted further investigation.

Case Presentation

Case 1. A Japanese woman had undergone esophagogastroduodenoscopy annually since her initial diagnosed of atrophic gastritis at 52 years of age (Fig. 1). The patient had a history of appendectomy, tonsillectomy, and hyperthyroidism. She had been taking no medications except for an antiallergic agent for her seasonal allergic rhinitis, which returned each spring and autumn. Although she tested negative for the serum anti-*H. pylori* IgG test, rod-shaped bacteria were detected in an endoscopic biopsy specimen obtained at age 62, at which time the urea breath test was positive at 4.8‰ (normal range, 0-2.4). The patient had thus undergone eradication treatment for *H. pylori* with first-line (rabeprazole, amoxicillin, and clarithromycin) and second-line (rabeprazole, amoxicillin, and metronidazole) drugs. Despite medical treatment, her urea breath test result was still positive (9.1‰). At 65 years of age, her urea breath test value increased to 84.4‰, and rod-shaped bacteria were pathologically observed again despite negative results for the stool antigen test for *H. pylori*. Therefore, vonoprazan, amoxicillin, and sitafloxacin were administered as third-line eradication treatments for her *H. pylori*-associated gastritis. Although the urea breath test performed four months after eradication still tested positive, the value had decreased to 2.7‰, close to the upper reference limit (2.4‰). No rod-shaped bacteria in the three biopsy specimens taken were detected on microscopy. Consequently, we concluded that the *H. pylori* infection had been eradicated.

The esophagogastroduodenoscopy that was performed when the patient was 69 years old revealed multiple small, white, granular deposits in her gastric fundus (Fig. 2A-C). Since the patient had not been taking proton pump inhibitors or vonoprazan, the scattered "deposits" were reinterpreted as tiny whitish protrusions, which are characteristic endoscopic features of autoimmune gastritis. Re-evaluation of the gastric mucosa revealed fundus and corpus-predominant atrophy (Fig. 2D), whereas the antrum was less affected by atrophic changes (Fig. 2E). Pathological evaluation of the endoscopic biopsy specimen with chromogranin A staining showed endocrine cell hyperplasia forming linear clusters and micro-nests. The patient tested positive for the presence of intrinsic factor antibodies and parietal cell antibodies. Her blood test results revealed a low pepsinogen I level at 4.3 ng/mL (normal, 28-100 ng/ml); with a normal pepsinogen II level of 7.2 ng/mL, her pepsinogen I/II ratio was also low, at 0.6. Her vitamin B12 was low as well, at < 100 pg/mL. Meanwhile, her red blood cell, hemoglobin, and hematocrit levels were all within the normal ranges. Therefore, the patient was diagnosed with autoimmune gastritis.

Case 2. A 38-year-old Japanese woman underwent an upper gastrointestinal series on a routine health checkup, which revealed an elevated lesion in her stomach. She was referred to our hospital for further evaluation. She had been taking propylthiouracil for five years for Graves' disease. Subsequent esophagogastroduodenoscopy revealed a reddish polyp in her gastric corpus (Fig. 3). She received a pathological diagnosis of hyperplastic polyps. Since then, she has been undergoing annual esophagogastroduodenoscopy. Although atrophy of the gastric mucosa was not initially found, it was found 3 years later. Based on her positive result for serum anti-*H. pylori* IgG, treatment with vonoprazan, amoxicillin, and clarithromycin was initiated, which resulted in the eradication of *H. pylori*. This was confirmed by a negative urea breath test result. At 47 years of age, esophagogastroduodenoscopy revealed a small flat white lesion in the gastric angle. Endoscopic biopsy was conducted, which revealed a diagnosis of signet ring cell carcinoma, which was successfully resected via endoscopic submucosal dissection.

Esophagogastroduodenoscopy performed six months after the endoscopic treatment of early gastric cancer revealed scattered tiny whitish protrusions in the gastric fornix and corpus (Fig. 4A-C). Flat to slightly elevated reddish areas were also identified in the fornix, cardia, and corpus (Fig. 4D). Corpus-predominant atrophy was also observed (Fig. 4E and 4F). Pathologically, linear endocrine cell hyperplasia was observed in the biopsy specimens from the reddish areas (Fig. 5). The diagnosis of autoimmune gastritis was confirmed by blood test results that were positive for parietal cell antibodies and showed a borderline-low level of pepsinogen I (28.7 ng/mL) and a low pepsinogen I/II ratio (1.1). The patient tested

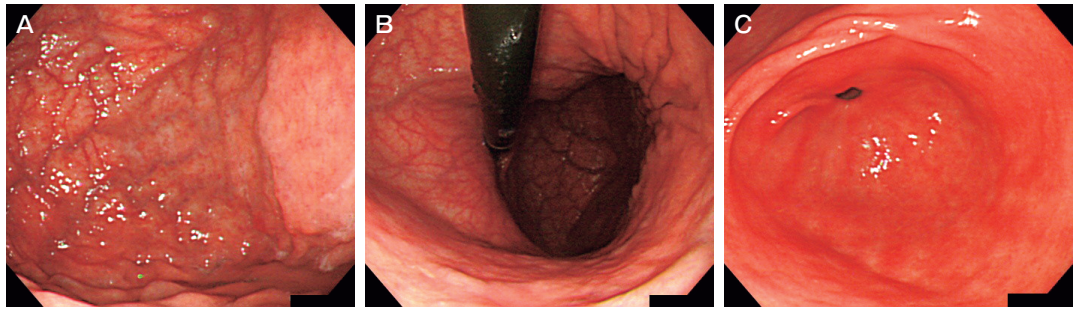

Fig. 1 Endoscopic images of Case 1 at the age of 52 years. Although she was diagnosed as having *H. pylori*-associated atrophic gastritis, retrospective re-evaluation of the endoscopy images revealed atrophy in the fornix (**A**) and corpus (**B**). This was in contrast to the common involvement of the antrum (**C**) in *H. pylori*-associated gastritus.

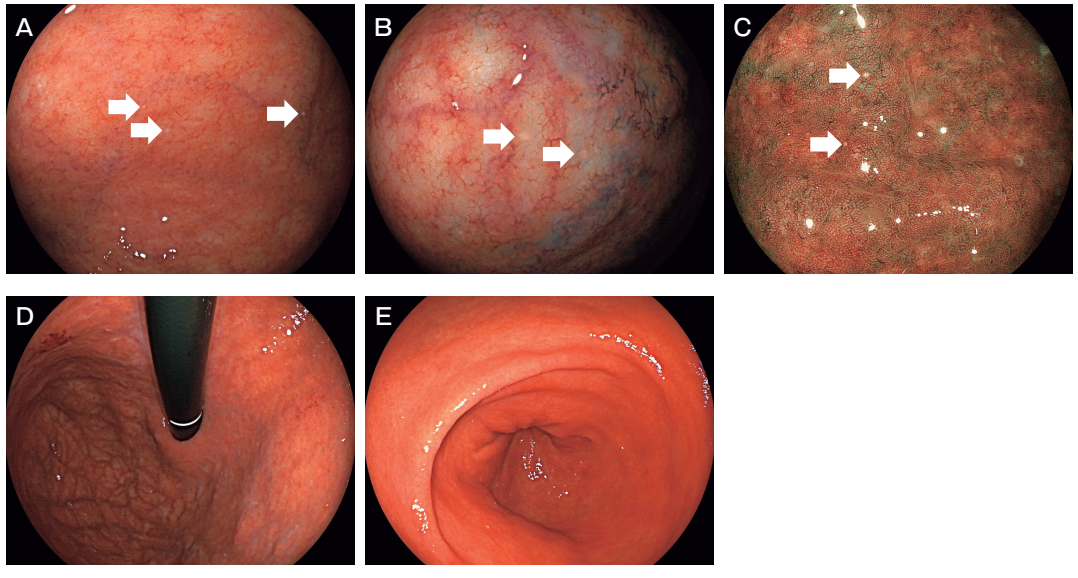

Fig. 2 Endoscopic images of Case 1 at the age of 69 years. Scattered minute whitish protrusions were observed in the gastric fundus (**A**–**C**, arrows; **A**, white light image; **B**, linked color imaging after indigo carmine dye spraying; **C**, blue laser imaging). There was corpus-predominant atrophy (**D**), while the antrum was less affected (**E**).

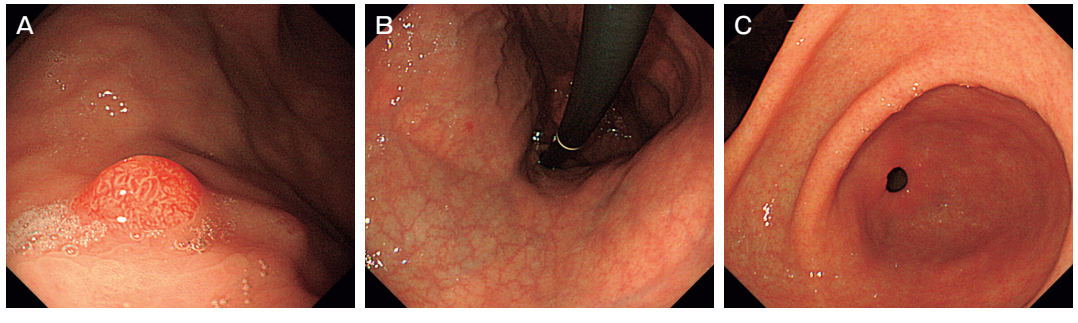

Fig. 3 Endoscopic images of Case 2 at the age of 38 years. A reddish hyperplastic polyp was observed in the gastric corpus (**A**). Although atrophy of the gastric mucosa was not initially noticed, re-evaluation of the endoscopic images revealed fornix- and corpus-dominant atrophy (**B**) and less involvement of the antrum (**C**).

negative for intrinsic factor antibodies.

Discussion

In the present two cases, the patients had received annual endoscopic exams for 17 and 9 years, respectively, without suspicion of autoimmune-etiology gastritis, until the discovery of scattered tiny whitish protrusions prompted us to perform further pathological evaluation of the gastric mucosa and serological testing, which ultimately led to the correct diagnosis of autoimmune gastritis. To our knowledge, this report is the first to describe patients with autoimmune gastritis having the discovery of this endoscopic feature as a turning point.

Multiple small, white lesions in the gastric mucosae of patients with autoimmune gastritis have been reported previously by several researchers, including ourselves [11,13]. Since this feature somewhat resembles the white globular lesions found within the margins of cancerous gastric epithelium [14,15], their endoscopic and pathological differentiation is important. Pathologically, the white globular appearance concomitant with cancer consists of dilated glands containing eosinophilic materials with necrotic epithelial fragments called intraglandular necrotic debris [14,15]. The epithelial lining of such glands is typically com-

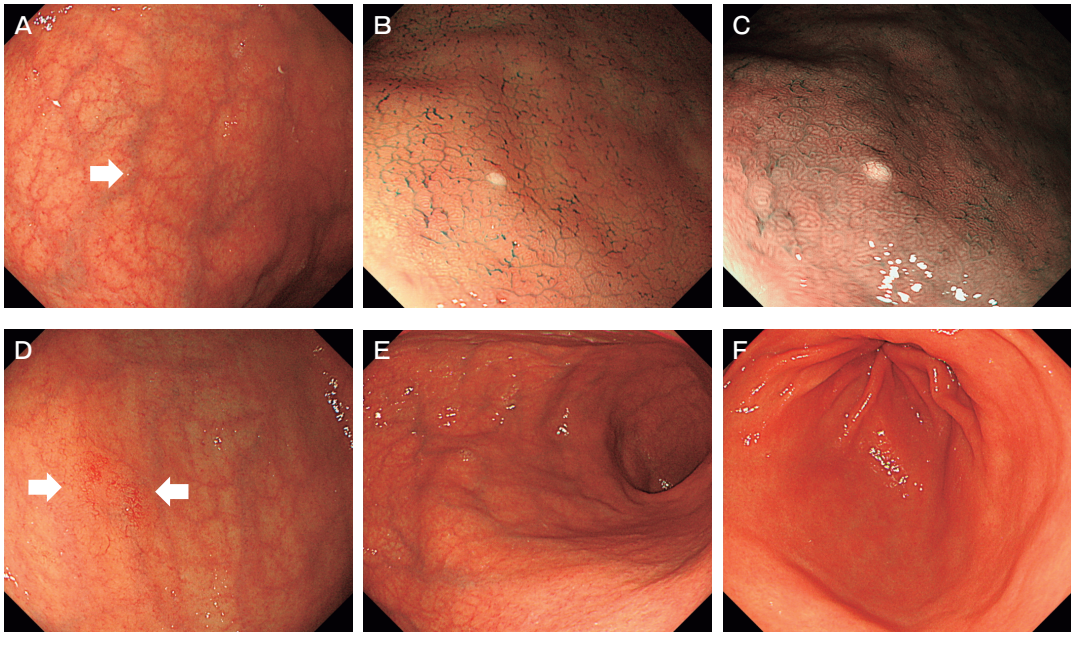

Fig. 4 Endoscopic images of Case 2 at the age of 47 years. Scattered minute whitish protrusions in the gastric fornix and corpus (**A**–**C**, arrow; **A**, white light image; **B**, magnifying observation after indigo carmine dye spraying; **C**, magnifying observation with narrow band imaging). A slightly elevated, reddish area was identified in the corpus (**D**). Mucosal atrophy was more prominent in the corpus (**E**) than in the antrum (**F**).

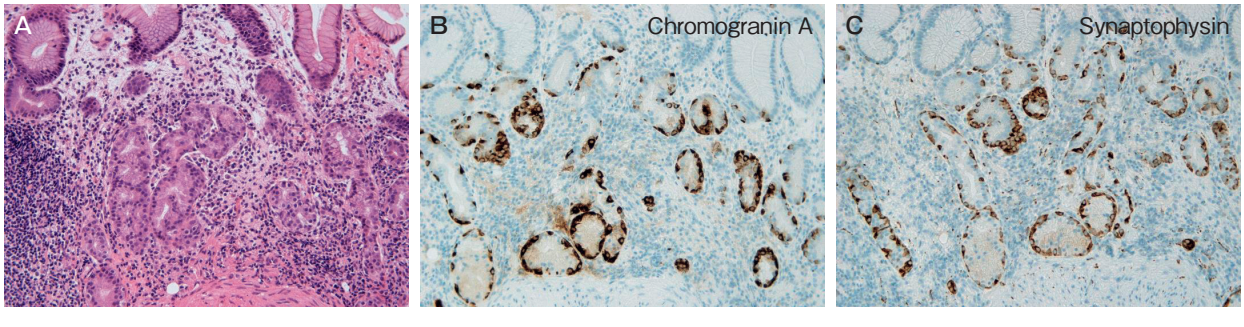

Fig. 5 Pathological images of Case 2. Biopsy from the stomach revealed linear endocrine cell hyperplasia that is positive for chromogranin A and synaptophysin. **A**, hematoxylin and eosin stain; **B**, chromogranin A stain; **C**, synaptophysin stain.

posed of cancer cells. In an earlier report, we described two other patients with autoimmune gastritis who presented with scattered minute whitish protrusions [13]. On microscopy, both cases showed cystic dilatation of the gastric glands containing mucus, with one also containing degenerated epithelial cells. Thus, the pathogeneses of the white globular lesions associated with cancerous mucosa and the scattered tiny whitish protrusions in autoimmune gastritis seem to be distinct.

Multiple small white substances have been reported in the gastric mucosae of those who use proton pump inhibitors or vonoprazan [16-18]. Cystically dilated glands were observed pathologically in the proton pump inhibitors or vonoprazan users. Consequently, although a white globular appearance associated with gastric cancer should be excluded first, endoscopists should also consider autoimmune gastritis or the use of proton pump inhibitor/vonoprazan when they find multiple white small lesions. As shown in the present two patients, this endoscopic feature can be a clue leading to the diagnosis of autoimmune gastritis, which can otherwise be overlooked for years.

It is easy to speculate that endoscopists might have simply missed the scattered tiny white protrusions on our patients' early endoscopic images, taken before undergoing *H. pylori* eradication, because this feature has only recently been described and reported. However, the characteristic tiny white protrusions could not be detected even after reevaluation of these images. There could be several possible reasons for this issue. The resolution of images produced by endoscopic probes has highly improved in the last decade. Thus, the quality of the endoscopy images might have been too low to identify scattered minute whitish protrusions. Another explanation, of course, is that the scattered minute whitish protrusions emerged after *H. pylori* eradication. Further careful examination of the stomach mucosa of patients with autoimmune gastritis during esophagogastroduodenoscopy will reveal the true nature of this endoscopic feature.

A multicenter survey involving Japanese patients with autoimmune gastritis revealed that 7.8% (17/218) tested positive for the *H. pylori* IgG antibody test [11]. In other studies, the prevalence of concurrent *H. pylori*-associated gastritis among patients with autoimmune gastritis was reported to be 20-50%. Several researchers have suggested that *H. pylori* may even be an etiological factor for autoimmune gastritis via molecular mimicry between *H. pylori* and the host, leading to the induction of autoreactive T cells [19]. Although it is unclear whether autoimmune gastritis developed as a sequela of chronic *H. pylori* infection in the present two patients, *H. pylori*-associated gastritis likely masked overlapping autoimmune gastritis, resulting in delayed diagnosis. Re-evaluation of the endoscopy images of the two patients revealed findings of corpus-predominant atrophy even several years prior to the diagnosis of autoimmune gastritis (Fig. 1 and Fig. 3).

In a large series of patients with autoimmune gastritis, scattered minute whitish protrusions were identified in 32.0% (71/222) [11]. Other characteristic endoscopic features of autoimmune gastritis have included sticky adherent dense mucus (72/222, 32.4%), remnant oxyntic mucosa (70/222, 31.5%), patchy redness (49/222, 22.1%), and circular wrinkle-like patterns (49/222, 22.1%). Multiple pseudopolyps presenting as reddish nodules on a background of gastric atrophy, which represented preserved oxyntic mucosa [20-22], and diffuse reddened, edematous gastric fundic gland mucosa, despite normal gastric pyloric gland mucosa [23], are features of early-stage autoimmune gastritis. Although the two patients in this study did not show any known features other than corpus-predominant atrophy and scattered minute whitish protrusions, awareness of these other endoscopic signs could facilitate prompt diagnosis of autoimmune gastritis [24].

It is also noteworthy that Case 1 had a history of hyperthyroidism, while Case 2 had Graves' disease. Autoimmune thyroiditis is a common comorbidity among patients with autoimmune gastritis. A multicenter study of Japanese patients with autoimmune gastritis revealed that 22.4% (55/245) had concomitant autoimmune diseases [11]. Chronic thyroiditis positive for thyroglobulin antibody was the most common comorbidity, accounting for 10.6% (26/245) of cases, followed by hyperthyroidism and other thyroid diseases (12/245, 4.9%). Thus, endoscopists should consider the possibility of autoimmune gastritis based on the occurrence of past or concurrent thyroid diseases. Conversely, once autoimmune gastritis is diagnosed, screening for other autoimmune diseases is required.

In Case 1, the urea breath test was positive, and the endoscopic biopsy specimen showed the presence of rod-shaped bacteria. However, serum IgG and stool antigen tests for *H. pylori* were negative. In addition, *H. pylori* eradication failed twice and succeeded on the

third attempt. Although we assumed *H. pylori* infection despite the negative results of *H. pylori*-specific antibody and antigen testing, another possible explanation is the colonization of urease-positive bacteria other than *H. pylori*. Furuta *et al.* reported that bacterial overgrowth with urease-producing organisms might cause false-positive results of urea breath tests in autoimmune gastritis patients [25]. They also reported that *H. pylori* eradication failed at least twice in 40 patients with autoimmune gastritis among 220 patients (18.2%). In the present patient, we were unable to determine whether the positive results of the urea breath test were caused by *H. pylori* or other bacteria. Although bacterial culture from the stomach is not a standard test for *H. pylori* diagnosis in Japan, analysis of gastric bacterial flora in autoimmune gastritis patients may reveal the role of *H. pylori* and other bacteria.

In conclusion, we present two patients with autoimmune gastritis. Although autoimmune gastritis had not been recognized over years of endoscopic monitoring in these two patients, the presence of scattered minute whitish protrusions in their gastric mucosa finally prompted further investigations, which ultimately led to the correct diagnosis of autoimmune gastritis. These cases indicate that understanding, awareness, and recognition of the endoscopic features specific to autoimmune gastritis are important for the prompt diagnosis of this disease.

References

1. Livzan MA, Gaus OV, Mozgovoi SI and Bordin DS: Chronic autoimmune gastritis: Modern diagnostic principles. Diagnostics (Basel) (2021) 11: 2113.
2. Kamada T, Maruyama Y, Monobe Y and Haruma K: Endoscopic features and clinical importance of autoimmune gastritis. Dig Endosc (2022) 34: 700–713.
3. Rustgi SD, Bijlani P and Shah SC: Autoimmune gastritis, with or without pernicious anemia: Epidemiology, risk factors, and clinical management: Ther Adv Gastroenterol (2021) 14: 17562848211038771.
4. Conti L, Annibale B and Lahner E: Autoimmune gastritis and gastric microbiota. Microorganisms (2020) 8: 1827.
5. Lenti MV, Rugge M, Lahner E, Miceli E, Toh BH, Genta RM, De Block C, Hershko C and Di Sabatino A: Autoimmune gastritis. Nat Rev Dis Primers (2020) 6: 56.
6. Weise F, Vieth M, Reinhold D, Haybaeck J, Goni E, Lippert H, Ridwelski K, Lingohr P, Schildberg C, Vassos N, Kruschewski M, Krasniuk I, Grimminger PP, Waidmann O, Peitz U, Veits L, Kreuser N, Lang H, Bruns C, Moehler M, Lordick F, Gockel I, Schumacher J, Malfertheiner P and Venerito M: Gastric cancer in autoimmune gastritis: A case-control study from the German centers of the staR project on gastric cancer research. United European Gastroenterol J (2020) 8: 175–184.
7. Lenti MV, Miceli E, Cococcia S, Klersy C, Staiani M, Guglielmi F, Giuffrida P, Vanoli A, Luinetti O, De Grazia F, Di Stefano M, Corazza GR and Di Sabatino A: Determinants of diagnostic delay in autoimmune atrophic gastritis. Aliment Pharmacol Ther (2019) 50: 167–175.
8. Kato M, Uedo N, Toth E, Shichijo S, Maekawa A, Kanesaka T, Takeuchi Y, Yamamoto S, Higashino K, Ishihara R, Nemeth A, Thorlacius H, Tomita Y and Wurm Johansson G: Differences in image-enhanced endoscopic findings between Helicobacter pylori -associated and autoimmune gastritis. Endosc Int Open (2021) 9: E22–E30.
9. Tsuboi M, Niikura R, Hayakawa Y, Hirata Y, Ushiku T and Koike K: Distinct features of autoimmune gastritis in patients with open-type chronic gastritis in Japan. Biomedicines (2020) 8: 419.
10. Kanzaki H, Uedo N, Ishihara R, Nagai K, Matsui F, Ohta T, Hanafusa M, Hanaoka N, Takeuchi Y, Higashino K, Iishi H, Tomita Y, Tatsuta M and Yamamoto K: Comprehensive investigation of areae gastricae pattern in gastric corpus using magnifying narrow band imaging endoscopy in patients with chronic atrophic fundic gastritis. Helicobacter (2012) 17: 224–231.
11. Terao S, Suzuki S, Yaita H, Kurahara K, Shunto J, Furuta T, Maruyama Y, Ito M, Kamada T, Aoki R, Inoue K, Manabe N, and Haruma K: Multicenter study of autoimmune gastritis in Japan: Clinical and endoscopic characteristics. Dig Endosc (2020) 32: 364–372.
12. Minalyan A, Benhammou JN, Artashesyan A, Lewis MS and Pisegna JR: Autoimmune atrophic gastritis: Current perspectives. Clin Exp Gastroenterol (2017) 10: 19–27.
13. Iwamuro M, Tanaka T, Kanzaki H, Kawano S, Kawahara Y and Okada H: Two cases of white globe appearance in autoimmune atrophic gastritis. Case Rep Gastrointest Med (2018) 2018: 7091520.
14. Yoshida N, Doyama H, Nakanishi H, Tsuji K, Tominaga K, Matsunaga K, Tsuji S, Takemura K, Yamada S, Tsuyama S, Katayanagi K and Kurumaya H: White globe appearance is a novel specific endoscopic marker for gastric cancer: A prospective study. Dig Endosc (2016) 28: 59–66.
15. Omura H, Yoshida N, Hayashi T, Miwa K, Takatori H, Tsuji H, Inamura K, Shirota Y, Aoyagi H, Masunaga T, Katayanagi K, Kurumaya H, Kaneko S and Doyama H: Interobserver agreement in detection of "white globe appearance" and the ability of educational lectures to improve the diagnosis of gastric lesions. Gastric Cancer (2017) 20: 620–628.
16. Iwamuro M, Tanaka T, Sakae H, Yamasaki Y, Kanzaki H, Kawano S, Kawahara Y and Okada H: Two cases of white globe appearance in non-cancerous stomach. Ecancermedicalscience (2018) 12: 856.
17. Nishiyama N, Kobara H, Kagawa S, Nishiyama A and Masaki T: Vonoprazan may cause white globe appearance in nonatrophic mucosa of stomach. Gastrointest Endosc (2021) 93: 767–768.
18. Miwa W, Hiratsuka T, Sato K, Fujino T and Kato Y: Development of white globe appearance lesions in the noncancerous stomach after vonoprazan administration: A report of two cases with a literature review. Clin J Gastroenterol (2021) 14: 48–58.
19. Kovacheva-Slavova MD, Angelov TA, Valkov HY, Iliev HI and Vladimirov BG: Current view on autoimmune gastritis. in: Gastritis - New Approaches and Treatments. Roesler BM, Ed. IntechOpen (2019) London.
20. Kotera T, Oe K, Kushima R and Haruma K: Multiple pseudopolyps presenting as reddish nodules are a characteristic endoscopic finding in patients with early-stage autoimmune gastritis. Intern Med (2020) 59: 2995–3000.
21. Ikeda T, Senoue I, Hara M, Tsutsumi Y, Harasawa S and Miwa T: Gastric pseudopolyposis: A new clinical manifestation of type A gastritis. Am J Gastroenterol (1985) 80: 82–90.
22. Krasinskas AM, Abraham SC, Metz DC and Furth EE: Oxyntic mucosa pseudopolyps: A presentation of atrophic autoimmune gastritis. Am J Surg Pathol (2003) 27: 236–241.
23. Kishino M, Yao K, Hashimoto H, Nitta H, Kure R, Yamamoto A, Yamamoto K, Nonaka K, Nakamura S and Tokushige K: A case of early autoimmune gastritis with characteristic endoscopic findings. Clin J Gastroenterol (2021) 14: 718–724.
24. Hirata Y: Endoscopy opens the door to a new era of autoimmune gastritis research. Dig Endosc (2020) 32: 323–325.
25. Furuta T, Baba S, Yamade M, Uotani T, Kagami T, Suzuki T, Tani S, Hamaya Y, Iwaizumi M, Osawa S and Sugimoto K: High incidence of autoimmune gastritis in patients misdiagnosed with two or more failures of H. pylori eradication. Aliment Pharmacol Ther (2018) 48: 370–377.