Multiple Pseudopolyps Presenting as Reddish Nodules are a Characteristic Endoscopic Finding in Patients with Early-stage Autoimmune Gastritis: A Report of Two Cases

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Abstract:
We herein report two cases of autoimmune gastritis without complete atrophy of the corpus. Both were positive for anti-parietal cell antibodies. Endoscopic examinations indicated that atrophic changes were predominant in the lesser curvature of the corpus in both cases. In one, the greater curvature was covered with pseudopolyp-like nodules, whereas the greater curvature of the other showed multiple similar nodules and mildly atrophic mucosa. Histopathological examinations of these nodules showed focal and patchy atrophy and preserved fundic glands with parietal cell pseudohypertrophy. Follow-up endoscopy and a repeated biopsy demonstrated the development of gastric atrophy on the greater curvature in both cases.

Key words: autoimmune gastritis, anti-parietal cell antibody, gastric pseudopolyp, parietal cell pseudohypertrophy

Introduction
Autoimmune gastritis (AIG) is a type of chronic atrophic gastritis associated with autoantibodies against parietal cells and intrinsic factors. The immune-mediated destruction of fundic glands leads to severe gastric mucosal atrophy limited to the corpus of the stomach. AIG with fully developed gastric mucosal atrophy, also known as type A gastritis (1), can be observed endoscopically and diagnosed histopathologically and serologically. Moderate or developing atrophy, however, is underdiagnosed because little is known about its endoscopic appearance.

We herein report two cases of AIG without fully developed gastric atrophy, focusing on their endoscopic and histopathological characteristics.

Case Reports
Case 1
A 48-year-old man underwent esophagogastroduodenoscopy (EGD) as part of an annual health checkup in July 2016. The patient had never received eradication therapy for Helicobacter pylori infection. He had been negative for serum anti-\textit{H. pylori} antibody (<3.0 U/mL) at his previous health checkup in July 2015. He was not taking any medicines including proton-pump inhibitors (PPIs) and antibiotics. Laboratory data showed the absence of anemia with a normal serum iron level (130 μg/dL). EGD showed atrophic changes limited to the lesser curvature of the lower to middle corpus but a normal mucosa in the antrum (Fig. 1a, b, c). Close-up views of the non-atrophic mucosa of the corpus showed a granular surface with slightly reddish nodules (Fig. 1d), which resembled pseudopolyps, one of the characteristic endoscopic findings of AIG (2). The pa-
Patient had undergone EGD for screening purposes in January 2015, with a biopsy sample taken from the greater curvature of the middle corpus, followed by a rapid urease test for the diagnosis of gastritis and *H. pylori* infection. The rapid urease test was negative. A retrospective examination of the biopsy specimen revealed non-atrophic fundic glands with mild infiltration of lymphocytes and eosinophils in the lamina propria and parietal cell pseudohypertrophy (Fig. 2a).

The patient was suspected of having AIG and tested for the presence of gastric autoantibodies and serum gastrin. He was positive for anti-parietal cell antibody (PCA), with a titer of 1:160, and his serum gastrin level was elevated (697 pg/mL), but he was negative for anti-intrinsic factor antibody (IFA). EGD performed in July 2018, showed no marked changes, although focal atrophy of the fundic glands was observed in biopsy specimens from the corpus (Fig. 2b). Parietal cell pseudohypertrophy was also observed. Immunohistochemical staining for synaptophysin demonstrated linear hyperplasia of enterochromaffin-like (ECL) cells (Fig. 2c). *H. pylori* was not detected immunohistochemically.

Subsequent EGD in June 2019, revealed the progression of atrophy on the greater curvature of the corpus. Gastric folds on the greater curvature had become flatter, and the number of slightly reddish nodules had decreased (Fig. 1e, f). The serum iron level remained normal (142 μg/dL). The PCA titer (1:640) was higher than that observed 3 years earlier, although the serum gastrin level remained unchanged (709 pg/mL). Biopsy specimens taken from the greater curvature of the corpus showed patchy atrophic changes in the fundic glands with increased lymphocyte infiltration and parietal cell pseudohypertrophy (Fig. 2d). Im-
munohistochemical staining for chromogranin A demonstrated linear and ring hyperplasia of ECL cells. These findings suggested that this patient had had early-stage AIG with active inflammation in 2015 that had progressed to gastric atrophy over the following four years.

**Case 2**

A 70-year-old woman underwent EGD for screening purposes in December 2017. She had never received eradication therapy for *H. pylori*. She was receiving medicines for type-2 diabetes mellitus but not a PPI. Endoscopic findings showed lesser curvature-predominant atrophy in the corpus with a normal antrum (Fig. 3a, b). Rows of slightly reddish nodules were observed on the longitudinal axis (Fig. 3b, c). Her serum was strongly positive for PCA, with a titer of 1:640, and was also positive for IFA. Her serum gastrin level was extremely high (5,265 pg/mL), but she was negative for anti-*H. pylori* antibody (<3.0 U/mL). Anemia was not observed. Anti-thyroglobulin (TgAb), anti-thyroid peroxidase (TPOAb) and anti-thyroid stimulating hormone receptor (TRAb) antibodies were negative (<10.0 U/mL, 11.0 U/mL and <1.0 IU/L, respectively). A biopsy specimen taken from the flat mucosa on the greater curvature revealed moderate atrophic changes with intestinal metaplasia. The nodules showed patchy atrophy and focal destruction of the fundic glands with infiltration of lymphocytes (Fig. 4a, b). *H. pylori* was not detected immunohistochemically.

Subsequent EGD in May 2019 showed the progression of gastric atrophy on the greater curvature of the corpus (Fig. 3d). The number and size of the slightly reddish nodules had decreased, and a biopsy specimen taken from the flat mucosa on the greater curvature showed atrophic changes, accompanied by the disappearance of the fundic glands. Patchy atrophy among the non-atrophic fundic glands was observed in the nodules. Immunohistochemical staining for chromogranin A demonstrated hyperplasia of ECL cells in the flat mucosa and nodules. The serum levels of iron and vitamin B12 were normal (67 μg/dL and 765 pg/mL, respectively). PCA was indeterminate due to the presence of a high titer (1:320) of anti-mitochondrial antibody (AMA) and was presumed to have decreased during the 2-year follow-up period. Her serum gastrin level remained extremely high (6,187 pg/mL). These findings suggested that this patient had had early-stage AIG in 2017 that had progressed to complete gastric atrophy over the next two years.

**Discussion**

This study describes two patients with AIG who showed...
changes over time in endoscopic and histopathological findings. These findings suggested that endoscopically observed reddish nodules are characteristic of early-stage AIG. Because many people in Japan undergo endoscopic examinations as part of routine health checkups, it is important to determine the endoscopic findings characteristic of AIG, a factor associated with high risks of both gastric neuroendocrine tumor and gastric cancer (2, 3). Although restricted atrophy of the lesser curvature of the corpus was not typical of AIG, as shown by the initial EGD findings in these two cases, both the unaffected antral mucosa and multiple nodular lesions on the rest of the corpus indicated the possibility

Figure 3. Endoscopic findings of Case 2 in December 2017 (a, b, c) and May 2019 (d). a: Normal antrum. b: Extensive mucosal atrophy on the lesser curvature of the corpus. c: Mild mucosal atrophy and nodules on the greater curvature of the corpus in December 2017. d: Progressive atrophy and reduced number of nodules on the greater curvature of the corpus in May 2019.

Figure 4. Histopathological findings of Case 2 in December 2017 (a, b). a, b: Patchy atrophy and lymphocytic destruction of the fundic glands in nodules on the greater curvature of the gastric corpus [Hematoxylin and Eosin staining, original magnification ×100 (a), ×200 (b)].
of early-stage AIG. PCA positivity, elevated serum gastrin levels, and histopathological findings supported the diagnosis of early-stage AIG. The endoscopic and histopathological findings on follow-up EGD two or three years later demonstrated the progression of gastric atrophy on the greater curvature in both cases.

Although AIG is thought to be uncommon in Japan, recent studies have reported an increase in its prevalence (2, 4-6). More than 90% of the cases were considered to have advanced AIG with corpus pan-atrophy in one of these studies (2). The diagnosis of AIG in the study relied on three criteria: endoscopic findings of advanced corpus-dominant atrophy, the presence of autoantibodies (PCA, or IFA) or pernicious anemia, and hypergastrinemia. Because the endoscopic characteristics of early-stage AIG have not yet been established, this condition is difficult to diagnose, although gastric pseudopolyps on a background of gastric atrophy may represent a preserved oxyntic mucosa, which is characteristic of AIG (7, 8). In case 1, non-atrophic areas of the gastric corpus were covered with nodular lesions mimicking gastric pseudopolyps at the time of the diagnosis. In case 2, similar nodular lesions were observed at the time of the diagnosis. A histopathological examination of these nodular lesions demonstrated focal or patchy atrophy among the non-atrophic fundic glands with mild lymphocyte infiltration and parietal cell pseudohypertrophy, factors consistent with the diagnostic criteria of AIG without advanced atrophy (9-11). ECL cell hyperplasia, a characteristic feature of AIG with advanced atrophy, was also identified immunohistochemically in nodular lesions. This was probably caused by an increase in the gastrin levels, as recently reported (11). In both cases, the nodular lesions shrank over time and were surrounded by atrophic mucosa, in agreement with the progression of gastric atrophy. Although a recent study reported that the histopathological progression of gastric atrophy from early-stage AIG occurred within three years, the relevant changes in the endoscopic appearances have not been determined (12). The findings in our cases indicate that the nodular lesions in non-atrophic areas of the gastric corpus are a manifestation of gastric inflammation and atrophy during the progress of early-stage AIG. The granular surface with nodular lesions in case 1 resembled a gastric cobblestone-like appearance, which is frequently observed in non-atrophic stomach following the long-term use of PPIs and is also accompanied by parietal cell pseudohypertrophy (13, 14). Although the serum gastrin levels and a PPI-induced gastric cobblestone-like appearance have not yet been found to be significantly correlated, the nodular lesions in case 1 likely resulted from reduced acid production and resultant hypergastrinemia.

Although studies have reported concurrent H. pylori infection in patients with AIG, as well as a positive association between the two (2-6), both of our cases were diagnosed as negative for H. pylori infection based on the absence of anti-H. pylori antibody, immunohistochemical findings, and their initial endoscopic examinations indicating that the antrum was unaffected. Whether or not H. pylori infection or its eradication affect the development of atrophy in cases with early AIG has been an issue of debate (3). To solve this issue, more cases and follow-up of early AIG cases with concurrent H. pylori infection are required.

AIG is associated with other autoimmune diseases, including autoimmune thyroiditis, type-1 diabetes mellitus, and primary biliary cholangitis (PBC) (15). Thyroid autoantibodies, such as TgAb, TPOAb, and TRAb, were negative in case 2, suggesting the absence of autoimmune thyroid diseases. These tests were not performed in case 1. AMA has recently been reported to be positive in 3.5% of AIG patients (16). In case 2, AMA was detected at a high level, in agreement with the overlapping staining patterns of AMA and PCA on rat tissue. Although the patient did not display specific symptoms, such as fatigue and pruritus, her alkaline phosphatase level (448 U/L) was above normal (reference range; 118-335 U/L). This patient should be followed up by assessing her liver biochemistry, taking probable PBC into consideration.

The assessment of additional cases, as well as a longer-term follow-up may enable the determination of the natural history of AIG.

The authors state that they have no Conflict of Interest (COI).

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