

Single Case

Evolving Autoimmune Gastritis Initially Hidden by Active *Helicobacter pylori* Gastritis

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Keywords

Autoimmune gastritis · *Helicobacter pylori* · Eradication

Abstract

Autoimmune gastritis (AIG) and *Helicobacter pylori* (*H. pylori*) gastritis are considered different diseases but exhibit overlapping features. We herein report a case of evolving AIG that had been initially hidden by active *H. pylori* gastritis. The patient was diagnosed with active *H. pylori* gastritis and received first-line eradication therapy in 2014 and successful second-line therapy in 2017. She was suspected of having early-stage AIG in 2019 based on the endoscopic finding of salmon roe-like nodular lesions on the greater curvature of the corpus. Parietal cell antibody was positive and the serum gastrin level was slightly elevated. Although subsequent endoscopy in 2020 revealed no significant changes in gastric atrophy, a sharp rise in the serum gastrin level was noted. A biopsy specimen taken from a nodular lesion showed pseudohypertrophy of residual parietal cells, lymphocytic infiltration, and enterochromaffin-like (ECL) cell hyperplasia. Upon retrospective reviews, endoscopic and serological findings obtained before eradication were consistent with active *H. pylori* gastritis. However, endoscopic salmon roe-like nodular lesions were detected in close-up views. In addition, lymphocytic destruction of fundic glands, pseudopyloric metaplasia, and ECL cell hyperplasia was histopathologically identified on a background of full-thickness inflammation, which suggested that early-stage AIG had coexisted with active *H. pylori* gastritis.

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Introduction

Atrophic gastritis traditionally falls into two main categories: type A and type B [1]. Type A gastritis is characterized by corpus-restricted gastric atrophy and the presence of parietal cell antibody (PCA) and is thus referred to as autoimmune gastritis (AIG). Type B gastritis exhibits multifocal gastric atrophy with antral involvement and is caused by long-standing *Helicobacter pylori* (*H. pylori*) infection. There is considerable overlap between the two types, and AIG can occur with current or past *H. pylori* infection. Most studies have focused on the involvement of *H. pylori* in AIG with fully developed gastric atrophy. Recent studies reported endoscopic features of early-stage AIG in cases without *H. pylori* infection [2–4]. However, there are no reports of endoscopic features of early-stage AIG in patients with current *H. pylori* infection. We herein report a case of evolving early-stage AIG initially hidden by active *H. pylori* gastritis, focusing on differences in endoscopic and histopathological findings before and after *H. pylori* eradication.

Case Report

A 64-year-old woman underwent esophagogastroduodenoscopy (EGD) as part of a health checkup at our hospital in December 2019. The patient had been diagnosed with gastritis and current *H. pylori* infection and had received first-line eradication therapy at a clinic in 2014. Successful eradication was confirmed after second-line therapy in 2017. The patient had never taken proton pump inhibitors except for the eradication therapies. EGD in 2019 showed atrophic changes in the antrum and lesser curvature of the corpus (Fig. 1a, b). The flat mucosa on the greater curvature of the corpus was slightly atrophic, while multiple nodular lesions were observed on the folds (Fig. 1c). In close-up views, the nodular lesions were lined up

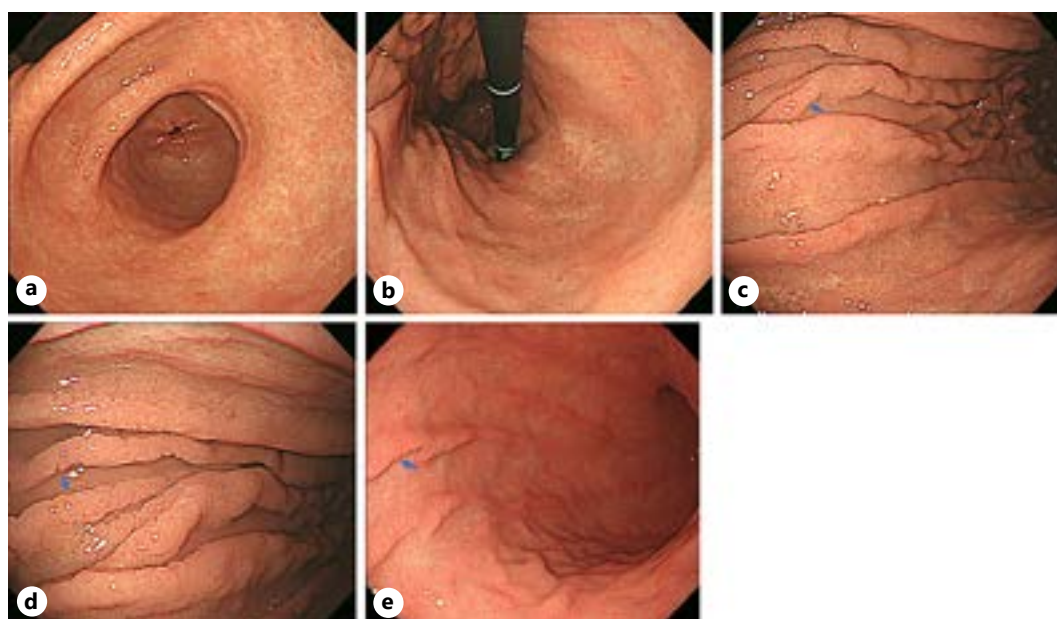


Fig. 1. Endoscopic findings in 2019 (a–d) and 2020 (e). **a, b** Mucosal atrophy in the antrum and lesser curvature of the corpus. **c** Nodular lesions on the folds in the greater curvature of the corpus (arrow) in 2019. **d** Close-up view of salmon roe-like nodular lesions on the folds (arrow). **e** Nodular lesions on the folds (arrow) in 2020.

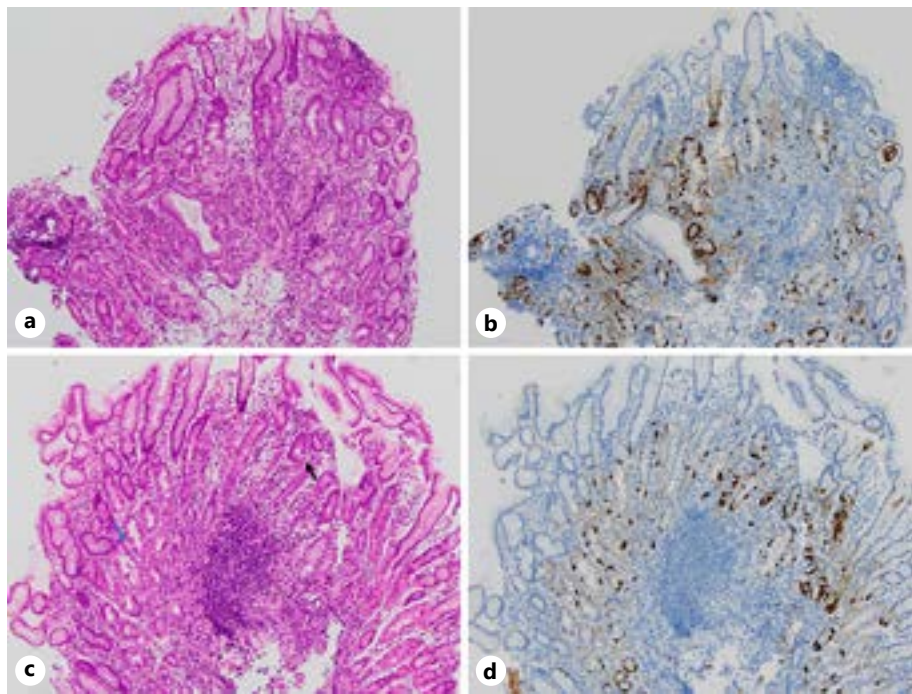


Fig. 2. Histopathological findings in 2020. **a, b** The flat mucosa in the greater curvature of the corpus shows atrophic changes of fundic glands with pseudopyloric metaplasia and linear hyperplasia of ECL cells. H&E staining, $\times 100$ (**a**), chromogranin A staining, $\times 100$ (**b**). **c, d** Nodular lesions in the greater curvature of the corpus show lymphocytic infiltration in the deep lamina propria, fundic gland destruction with associated apoptosis (black arrow), and pseudohypertrophy of residual parietal cells (blue arrow). (H&E, $\times 100$ (**c**), chromogranin A staining, $\times 100$ (**d**)). H&E, hematoxylin and eosin.

in rows like salmon roe (Fig. 1d) and resembled pseudopolyps in early-stage AIG without *H. pylori* infection [2]. PCA was strongly positive with a titer of 1:320, and the serum gastrin level was slightly elevated (540 pg/mL). Anti-*H. pylori* antibody was high-negative with a titer of 6.9 U/mL. The patient was suspected of having AIG coexisting with post-eradicated *H. pylori* gastritis.

Subsequent EGD in December 2020 revealed no significant progression of atrophy in the greater curvature of the corpus, with nodular lesions remaining on the folds (Fig. 1e). The serum gastrin level had increased to 1,067 pg/mL, while the PCA titer remained unchanged (1:320). Biopsy specimens were taken from the flat mucosa and a nodular lesion on the folds in the greater curvature of the corpus. Foveolar hyperplasia and atrophic changes of fundic glands with pseudopyloric metaplasia were observed in the flat mucosa (Fig. 2a). Linear hyperplasia of enterochromaffin-like (ECL) cells was detected by chromogranin A immunostaining (Fig. 2b). *H. pylori* immunostaining was negative. Atrophic changes were milder in the nodular lesion than in the flat mucosa. Dense lymphocytic infiltration in the deep lamina propria, fundic gland destruction with associated apoptosis, and pseudohypertrophy of residual parietal cells were observed. Pseudopyloric metaplasia and ECL cell hyperplasia were sparsely distributed (Fig. 2c, d). These findings supported the diagnosis of early-stage AIG coexisting with post-eradicated *H. pylori* gastritis.

We retrieved and retrospectively reviewed endoscopic, serological, and histopathological findings that had been obtained at the clinic before successful *H. pylori* eradication. EGD images in 2014 showed mucosal atrophy, diffuse redness, enlarged folds, and sticky mucus (Fig. 3a), consistent with the endoscopic hallmarks of current *H. pylori* infection described in the Kyoto

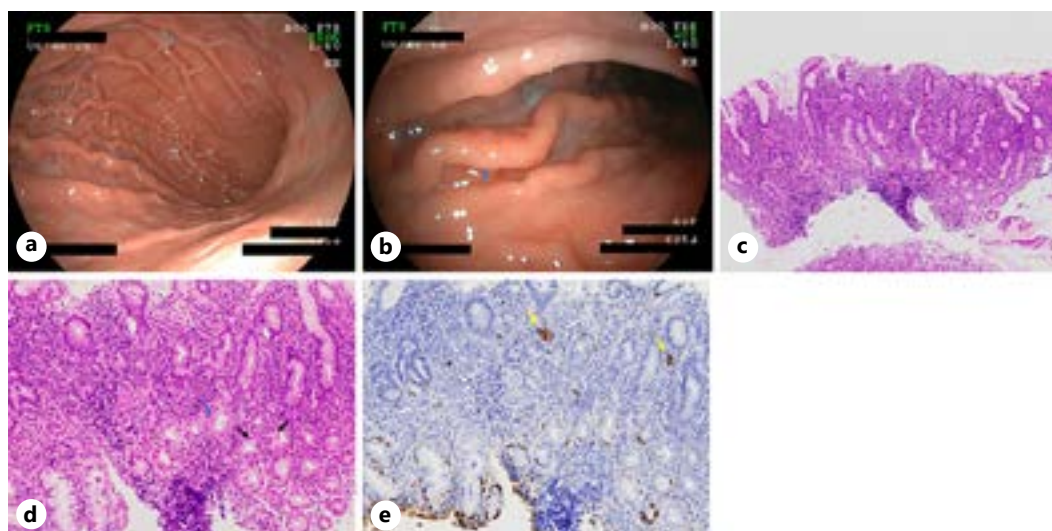


Fig. 3. Endoscopic and histopathological findings in 2014. **a** Enlarged folds and sticky mucus in the greater curvature of the corpus. **b** Close-up views of salmon roe-like nodular lesions on the folds (arrow). **c** A low-power view shows full-thickness inflammation in the greater curvature of the corpus (H&E, $\times 100$). **d** A high-power view shows parietal cell pseudohypertrophy (blue arrow), pseudopyloric metaplasia and fundic gland destruction with apoptosis (black arrow) (H&E, $\times 200$). **e** Nodular hyperplasia of ECL cells (yellow arrow) (chromogranin A staining, $\times 200$).

Classification of Gastritis [5]. Nodular lesions, resembling those observed in 2019, were detected on the folds in the greater curvature of the corpus, but only in close-up views (Fig. 3b). Anti-*H. pylori* antibody was positive (21.2 U/mL). EGD findings in 2017, 3 years after first-line eradication therapy, were similar to those in 2014, including nodular lesions, and anti-*H. pylori* antibody was still positive, suggesting that first-line eradication therapy had failed. Second-line eradication therapy in 2017 was successful, as confirmed by a negative urea breath test (0.5 ‰). The original biopsy specimens obtained from the folds in the greater curvature of the corpus in 2014 showed full-thickness inflammation of the fundic gland mucosa with lymphocytes, plasmacytes, and neutrophils (Fig. 3c), and were positive for *H. pylori* by Giemsa staining. Closer observation revealed lymphoid aggregates, parietal cell pseudohypertrophy, pseudopyloric metaplasia, and fundic gland destruction with associated apoptosis in the deep lamina propria (Fig. 3d), which raised the possibility of concomitant early-stage AIG at that time. Additional chromogranin A staining detected nodular ECL cell hyperplasia (Fig. 3e). Taken together, these findings suggest that evolving early-stage AIG had been hidden on a background of active *H. pylori* gastritis and became apparent 3 years after successful eradication.

Discussion

Endoscopic diagnosis of early-stage AIG was recently addressed in *H. pylori*-uninfected cases [2–4]. However, it is challenging to recognize early-stage AIG on a background of active *H. pylori* gastritis. We describe a case of early-stage AIG that had been initially hidden by active *H. pylori* gastritis and subsequently revealed after eradication. This report highlights two important clinical issues. First, characteristic histopathological features of early-stage AIG, including ECL cell hyperplasia, could be identified on the background of concomitant active *H. pylori* gastritis. Second, early-stage AIG coexisting with *H. pylori* gastritis could present

with salmon roe-like nodular lesions on the folds in the greater curvature of the corpus, which resembled a characteristic endoscopic feature of *H. pylori*-uninfected early-stage AIG. These histopathological and endoscopic findings became evident after eradication.

Although histopathological and immunohistochemical features of early-stage AIG have been clarified [6], differences in these features between patients with and without *H. pylori* infection have not been analyzed. A recent study proposed histopathological and immunohistochemical criteria to identify AIG in cases with active *H. pylori* infection, namely, a combination of full-thickness inflammation, oxyntic gland destruction, and ECL cell hyperplasia [7]. Our case was diagnosed with active *H. pylori* gastritis 6 years before the biopsy-confirmed diagnosis of early-stage AIG. Retrospective evaluation of the original biopsy specimen taken before eradication revealed transmucosal inflammation, lymphocytic destruction of fundic glands, and pseudopyloric metaplasia in the deep lamina propria. Hyperplasia of ECL cells was observed by chromogranin A staining. These findings met the proposed criteria [7]. In addition, lymphocytic infiltration of fundic glands was accompanied by apoptotic bodies. Apoptotic cell loss reflects the autoimmune process in experimental AIG [8] and human AIG [9]. Hence, these histopathological and immunohistochemical findings in 2014 suggested that early-stage AIG had coexisted with active *H. pylori* gastritis, despite the lack of serological studies for AIG at that time.

Multiple nodular lesions on the greater curvature of the gastric corpus are a characteristic endoscopic feature of *H. pylori*-uninfected early-stage AIG [2]. In our case, EGD in 2019 showed similar endoscopic findings (salmon roe-like nodular lesions) on the background of post-eradicated *H. pylori* gastritis. These nodular lesions were less atrophic than the surrounding nonpolypoid mucosa, and parietal cell pseudohypertrophy was observed in residual fundic glands. These histopathological findings suggested that the nodular lesions were remnants of the oxyntic mucosa presenting as pseudopolyps [10]. Although atrophic changes were present in the antrum, the possibility of early-stage AIG was considered. Positivity for PCA, an increased serum gastrin level, and histopathological findings supported the diagnosis. Endoscopic findings of early-stage AIG in *H. pylori*-uninfected patients include a normal antrum and a homogenous, diffuse spread of salmon roe-like nodular lesions in the greater curvature of the corpus [2], which can assist diagnosis. However, in our case with post-eradicated gastritis, the nodular lesions in close-up views were irregular in size, shape, and distribution. It was even harder to recognize them on the background of enlarged folds with active *H. pylori* gastritis. Therefore, in cases with *H. pylori* infection such as the present case, it is difficult to detect early-stage AIG without careful examinations of EGD findings in the gastric corpus. Further studies with additional cases and a longer follow-up period after eradication are required.

Although some cases with AIG have current or past *H. pylori* infection, the exact relationship between the status of *H. pylori* infection and AIG has not been clarified. It remains controversial whether *H. pylori* infection plays a positive or negative role in the development of AIG in experimental mouse models [11, 12]. Clinical studies conducted in Japan reported that the prevalence of current *H. pylori* infection was low among AIG patients with corpus pan-atrophy [10, 13] and nearly half of the AIG cases were post-eradicated in 1 study [13]. These results imply that endoscopic identification of AIG with fully developed gastric atrophy is harder among patients with active *H. pylori* gastritis than among those with post-eradicated gastritis. There are conflicting reports regarding the effects of *H. pylori* eradication on the development of AIG [14–16]. Although the existence of early-stage AIG became evident after eradication in our case, neither EGD nor biopsy specimens after eradication provided enough evidence of significant progression of gastric atrophy compared with those before eradication. It is possible that *H. pylori*-dependent early-stage AIG can be sustained by a tiny amount of residual *H. pylori* after successful eradication. We cannot exclude another possibility that elimination of active inflammation in the fundic mucosa by eradication simply uncovered early-stage AIG that had developed independently of active *H. pylori* gastritis. However, the sharp increase in the gastrin

level from 540 pg/mL in 2019 to 1,067 pg/mL in 2020 suggested that destruction of parietal cells was accelerated after eradication. Further cases must be studied to determine whether eradication of *H. pylori* is the driving force for the development of evolving AIG.

In conclusion, early-stage AIG can be hidden by active *H. pylori* gastritis and endoscopic salmon roe-like nodular lesions can assist diagnosis in some cases. Histopathological examinations of biopsy specimens from the corpus are recommended in such cases. Lymphocytic destruction of fundic glands and pseudopyloric metaplasia in combination with full-thickness inflammation raise the possibility of early-stage AIG.

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Statement of Ethics

We have reported this case in compliance with the Declaration of Helsinki. Informed written consent was obtained from the patient for publication of this case report and any accompanying images. This study protocol was reviewed and the need for approval was waived by the Ethics Committee of Uji-Tokushukai Medical Center.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

T. Kotera wrote the draft of this manuscript. U. Yoshioka, T. Takemoto, and T. Kotera acquired the data. R. Kushima analyzed the pathological findings. K. Haruma supervised this case report.

Data Availability Statement

All data analyzed during this study are included in this article. Further enquiries can be directed to the corresponding author.

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