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【 CASE REPORT 】

An Evaluation of Endoscopic Images from Over 15 Years Prior to the Diagnosis of Autoimmune Gastritis: A Report of Three Patients

Maki Ayaki[1], Noriaki Manabe[1], Masayuki Murota[2], Minoru Fujita[1] and Ken Haruma[3]

Abstract:
We herein describe three patients whose endoscopic images from over 15 years prior to their diagnosis of autoimmune gastritis (AIG) were available for review. All patients had corpus-dominant atrophic gastritis at the time of the diagnosis of AIG. Previous endoscopic images without severe atrophy showed erythema restricted to the fundic mucosa. These findings are suggestive of ongoing gastritis in patients with AIG. Initial endoscopy in Patient 2 showed multiple hyperplastic polyps that decreased in size and number over the course of 15 years. In this patient, circular wrinkle-like patterns and remnant oxyntic mucosa were visible after the atrophy had become quite prominent.

Key words: autoimmune gastritis, endoscopic image, iron deficiency anemia, early phase, Hashimoto's thyroiditis

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Introduction

Autoimmune gastritis (AIG) is a chronic inflammatory disease in which destruction of the parietal cells of the gastric corpus causes defective secretion of essential substances, such as pepsin, hydrochloric acid, and intrinsic factor, leading to digestive complications (1). A typical endoscopic finding of AIG is corpus-dominant severe atrophic gastritis, also called "endoscopic reversed type atrophic gastritis" (2). In recent years, endoscopic images of AIG without atrophy, known as early-phase AIG or pre-atrophic-stage AIG, have attracted attention, and several case reports have been published (3-5).

We attempted to elucidate the long-term course of AIG by reviewing the medical records of patients with a confirmed diagnosis of AIG. We herein report three patients with AIG whose endoscopic images from over 15 years prior to their AIG diagnosis were available for review.

Case Report

We retrospectively reviewed the clinical course of AIG in 3 patients using medical records covering a course of over 15 years among 18 patients with a definitive diagnosis of AIG at our hospital from 2018 to 2020. In all three patients, endoscopic findings of corpus-predominant severe atrophic gastritis led to the final diagnosis of AIG. The definition of AIG in these patients was based on the following criteria from a previous study (6): endoscopic corpus-predominant severe atrophic gastritis, gastric anti-parietal cell antibody (APCA) positivity, and hypergastrinemia (>350 pg/mL) with no history of proton pump inhibitor therapy.

Informed consent or a substitute for it was obtained from all patients for inclusion in the study.

Patient 1

A 71-year-old woman with a history of Hashimoto's disease was suspected of having AIG because of corpus-

[1]Division of Endoscopy and Ultrasonography, Department of Clinical Pathology and Laboratory Medicine, Kawasaki Medical School, Japan, [2]Department of Gastroenterology, Sakaide City Hospital, Japan and [3]Division of Gastroenterology, Department of Internal Medicine 2, Kawasaki Medical School, Japan
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Correspondence to Dr. Maki Ayaki, mkmnb1979@yahoo.co.jp

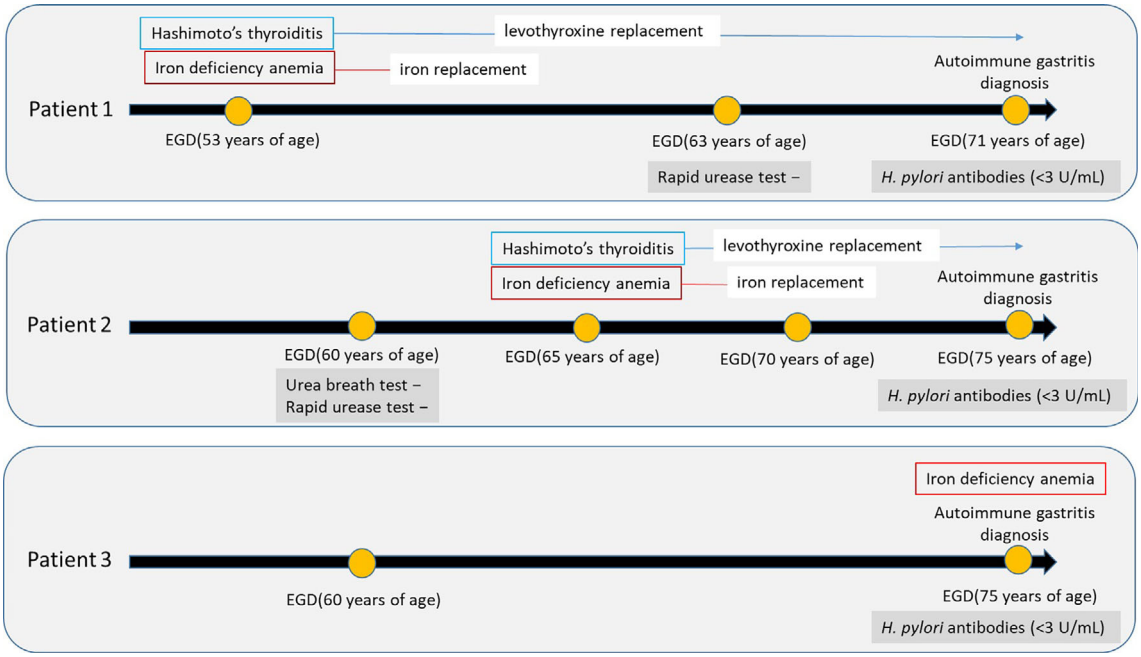

Figure 1. Schematic illustration of the clinical course of the three patients. The orange circle represents the timing of the esophagogastroduodenoscopy procedures shown in Figs. 2 to 5.

dominant advanced atrophic gastritis. She was confirmed to have AIG after undergoing histological and serological tests, which revealed the following: serum gastrin level, 2,130 pg/mL (reference range, <200 pg/mL); APCA level, ×80 positive; and IgG antibodies to *Helicobacter pylori*, <3 U/mL. Anemia was not observed at the time of the diagnosis of AIG, and the serum levels of iron and vitamin B12 were within the reference ranges (77 μg/dL and 785 pg/mL, respectively).

The patient was diagnosed with Hashimoto's thyroiditis and iron deficiency anemia [hemoglobin, 9.2 g/dL; mean corpuscular volume (MCV), 69 fL; iron, 17 μg/dL; and ferritin, 3.3 ng/mL] 18 years prior to her diagnosis of AIG (Fig. 1). Levothyroxine replacement therapy was started for treatment of the Hashimoto's thyroiditis, and a clinical workup for blood loss was begun to identify the cause of the iron deficiency anemia. In addition, she had undergone an initial endoscopic examination at that time. The cause of the iron deficiency anemia was unknown, and she continued to undergo regular endoscopic examinations every year thereafter; we were thus able to retrospectively evaluate the changes in her endoscopic images over an 18-year period (Fig. 2). The initial image showed no obvious change in the gastritis, but the image obtained 8 years before presentation to our hospital (63 years old) showed redness, suggesting the presence of gastritis. At that time, *H. pylori*-associated gastritis was suspected, but a rapid urease test was negative.

Her unexplained iron deficiency anemia was treated with oral administration of iron supplements (ferrous fumarate: elemental iron 100 mg/day). Her hemoglobin recovered to 12 g/dL, and the oral iron administration was discontinued 6 months after the normalization of the hemoglobin level. She developed no recurrence of anemia over the course of 18 years.

Patient 2

A 75-year-old woman with a history of Hashimoto's thyroiditis underwent upper gastrointestinal endoscopy for follow-up of hyperplastic polyps. The endoscopic examination revealed multiple hyperplastic polyps on the greater curvature of the gastric corpus (Fig. 3a). A flat elevated lesion of about 20 mm in size was observed near the gastric cardia (Fig. 3b). Magnifying endoscopic examination revealed closely arranged small, round pits, indicating island-shaped type remnant oxyntic mucosa (6) (Fig. 3c). No atrophy or inflammation was present; however, a circular wrinkle-like pattern (6) was seen in the antrum (Fig. 3d). These endoscopic findings prompted us to suspect AIG.

A serological examination showed that the APCA level was ×80 positive, gastrin level was 4,130 pg/mL, and *H. pylori* IgG antibody level was <3 U/mL. These findings supported the diagnosis of AIG.

She did not have anemia, and her iron and vitamin B12 levels were within the reference ranges at the time of AIG diagnosis. The patient had undergone her first endoscopic examination 15 years previously at 60 years old. Hyperplastic polyps were found in the gastric body (Fig. 4), and *H. pylori*-associated gastritis was suspected at that time. However, a urea breath test and rapid urease test were negative, and the cause of the hyperplastic polyps was unknown. She had undergone regular endoscopic examinations for the purpose of follow-up of the hyperplastic polyps. New hyperplastic polyps had appeared in the anterior wall of the lower body 5 years previously, at 70 years old. The endoscopic findings at 75 years old (when she was diagnosed with AIG) showed that the size and number of hyperplastic polyps had

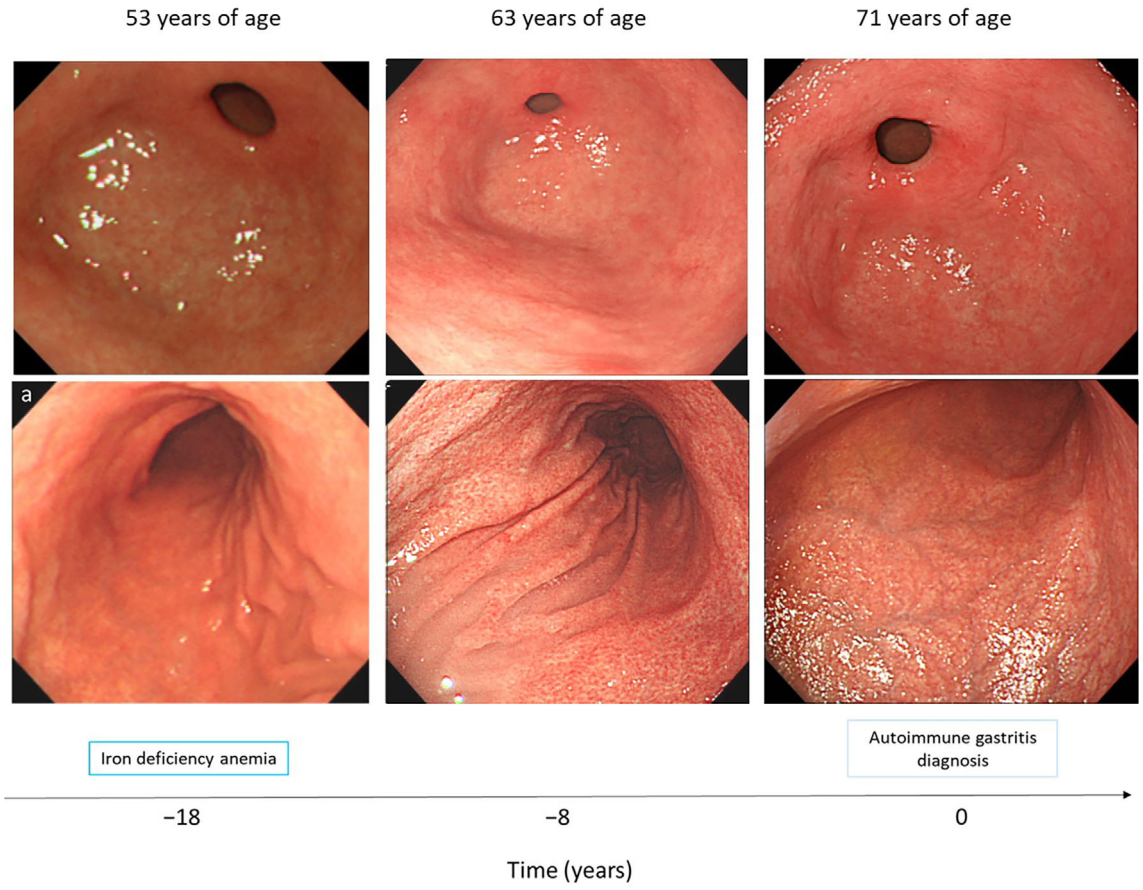

Figure 2. Changes in endoscopic findings of Patient 1. a: Endoscopic findings at 53 years old (18 years before presentation). Iron deficiency anemia was present, even in the absence of severe atrophic gastritis. b: Endoscopic findings at 63 years old (8 years before presentation). Diffuse erythema was observed in the fundic mucosa. c: Endoscopic findings at the time of the diagnosis (71 years old). The folds had disappeared, and severe atrophic gastritis was observed in the corpus.

decreased (Fig. 4).

The patient's medical records showed that fatigue had initially developed at 65 years old, and a thorough examination revealed Hashimoto's thyroiditis and iron deficiency anemia (hemoglobin, 9.7 g/dL; MCV, 72 fL; iron, 32 μg/dL; and ferritin, 2.4 ng/mL). She was treated with levothyroxine replacement and oral iron replacement (ferrous citrate: elemental iron 100 mg/day) for 3 months to increase her hemoglobin level to the normal range. Iron supplements were administered for 15 months and subsequently discontinued; however, she developed no relapse of anemia (Fig. 1).

Patient 3

A 75-year-old woman with a history of hypertension and no history of autoimmune disease was referred to our hospital for the evaluation of iron deficiency anemia (hemoglobin, 9.8 g/dL; MCV, 71 fL; iron, 17 μg/dL; ferritin, 3.8 ng/mL; and VitB12, 525 pg/mL). Computed tomography and colonoscopy were unremarkable; however, upper gastrointestinal endoscopy revealed severe atrophic gastritis restricted to the corpus (Fig. 5). A serum analysis revealed high levels of gastrin (3,560 pg/mL; reference range, <200 pg/mL), APCAs (×320 positive), and *H. pylori* antibodies (<3 U/mL) with no history of eradication. Endocrine cell micronests were confirmed in the tissue sample from the corpus, leading to a definitive diagnosis of AIG. Other than AIG, there were no abnormal findings that could explain the iron deficiency anemia. After 2 months of oral iron therapy (ferrous fumarate: elemental iron 100 mg/day), the patient's hemoglobin improved to 13.6 g/dL. The iron therapy was subsequently discontinued, and the anemia did not recur.

The patient had undergone endoscopy 15 years previously, and the mucosa of the gastric body was swollen in the gastric area with erythema in the greater curvature (Fig. 5). However, no overt gastritis was observed in the antrum (Fig. 5). An examination of *H. pylori* infection was not carried out because it was not covered by the National Health Insurance System of Japan at that time. However, no enlarged folds or sticky mucus, such as those seen in *H. pylori*-associated active gastritis, were found.

Discussion

AIG is a progressive chronic inflammatory disease in

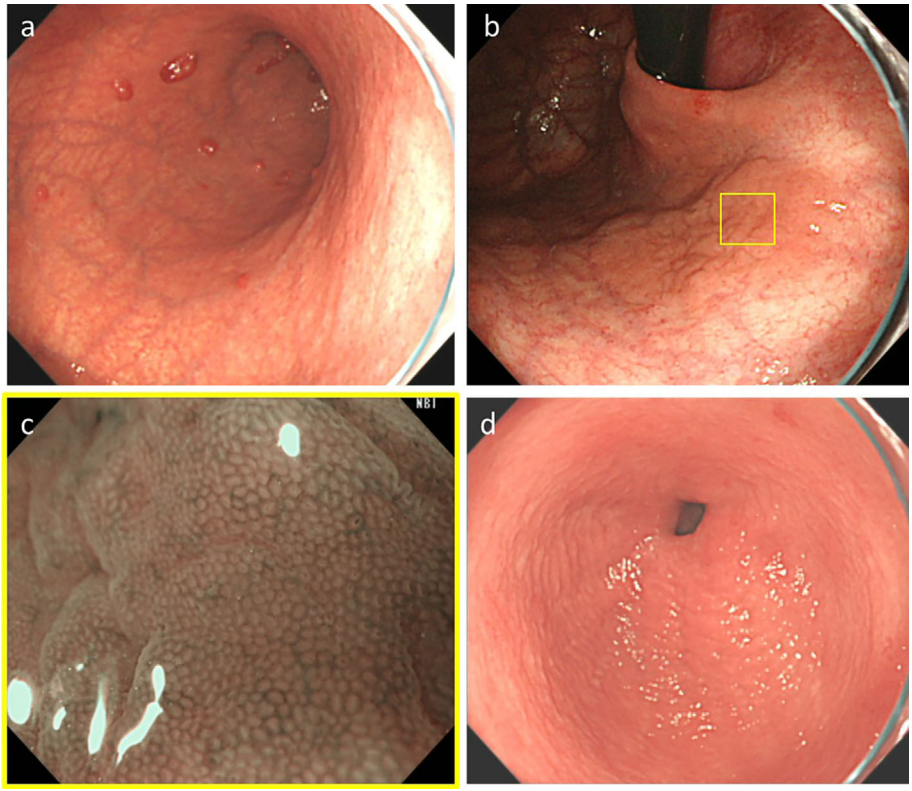

Figure 3. **Endoscopic findings at the time of the diagnosis in Patient 2. a: Multiple hyperplastic polyps were seen in the corpus. b: Remnant oxyntic mucosa without destruction of the gastric fundic glands in the anterior wall of the upper body was observed. c: Magnifying endoscopic appearance of the remnant oxyntic mucosa in the yellow square of Fig. 2b. d: No atrophy was present, but a circular wrinkle-like pattern was observed in the antrum.**

which parietal cells in the stomach are destroyed by autoimmune mechanisms. AIG is localized to the gastric corpus and fundus (type A gastritis) (7), and it differs from the type B gastritis caused by *H. pylori* (1).

In the three patients reported here, the previous endoscopic images showed erythema and hyperplastic polyps in the gastric body suggestive of active gastritis, and *H. pylori* gastritis was suspected at that time. It is very difficult to distinguish between *H. pylori*-active gastritis and active-stage AIG when only the corpus is observed (5, 8). A careful assessment of the antrum is required to distinguish between these two types of gastritis. *Helicobacter pylori* gastritis is most intense in the antrum and typically develops in the corpus (9). Unfortunately, no histological or serological tests were performed in the past in these patients; therefore, we were unable to determine when these patients developed AIG. In retrospect, however, all three patients in this series had longstanding chronic gastritis with sparing of the antral mucosa, suggesting that they had had AIG long before the diagnosis of AIG was actually made.

Two interesting results were obtained in this study. First, we observed changes in the endoscopic images of the hyperplastic polyps, remnant oxyntic mucosa, and a circular wrinkle-like pattern, which are known endoscopic findings in patients with AIG. For Patient 2, all three findings were present at the time of the diagnosis. A retrospective examination revealed that the hyperplastic polyps, which are strongly associated with gastritis (10), had already been present before the 15-year observation period. Some of these hyperplastic polyps had decreased in size over the 15-year period, while others had disappeared completely. The pathogenesis of gastric hyperplastic polyps is still unknown, but it is suggested that the exaggerated repair of mucosal damage and hypergastrinemia may play a role in the development of polyps (10). AIG-related inflammation is thought to subside as the target of the autoimmune response gradually disappears (11). Therefore, the shrinkage of these hyperplastic polyps in Patient 2 may indicate a reduced degree of gastritis-associated inflammation. The remnant oxyntic mucosa near the cardia was not clear 15 years ago but became visible 10 years later and eventually became clearer. A circular wrinkle-like pattern is a recently reported new endoscopic appearance of the anal mucosa in 22% of patients with AIG (6). This finding was not present 15 years ago but appeared 10 years later and persisted for 5 years. The course of the endoscopic images of Patient 2 suggests that hyperplastic polyps are an early sign of AIG, whereas remnant oxyntic mucosa or a circular wrinkle-like pattern may be a sign of progressed atrophy.

The other interesting result is the timing of the appearance of iron deficiency anemia. Only one patient (Patient 3) had iron deficiency anemia at a progressed stage of atrophy.

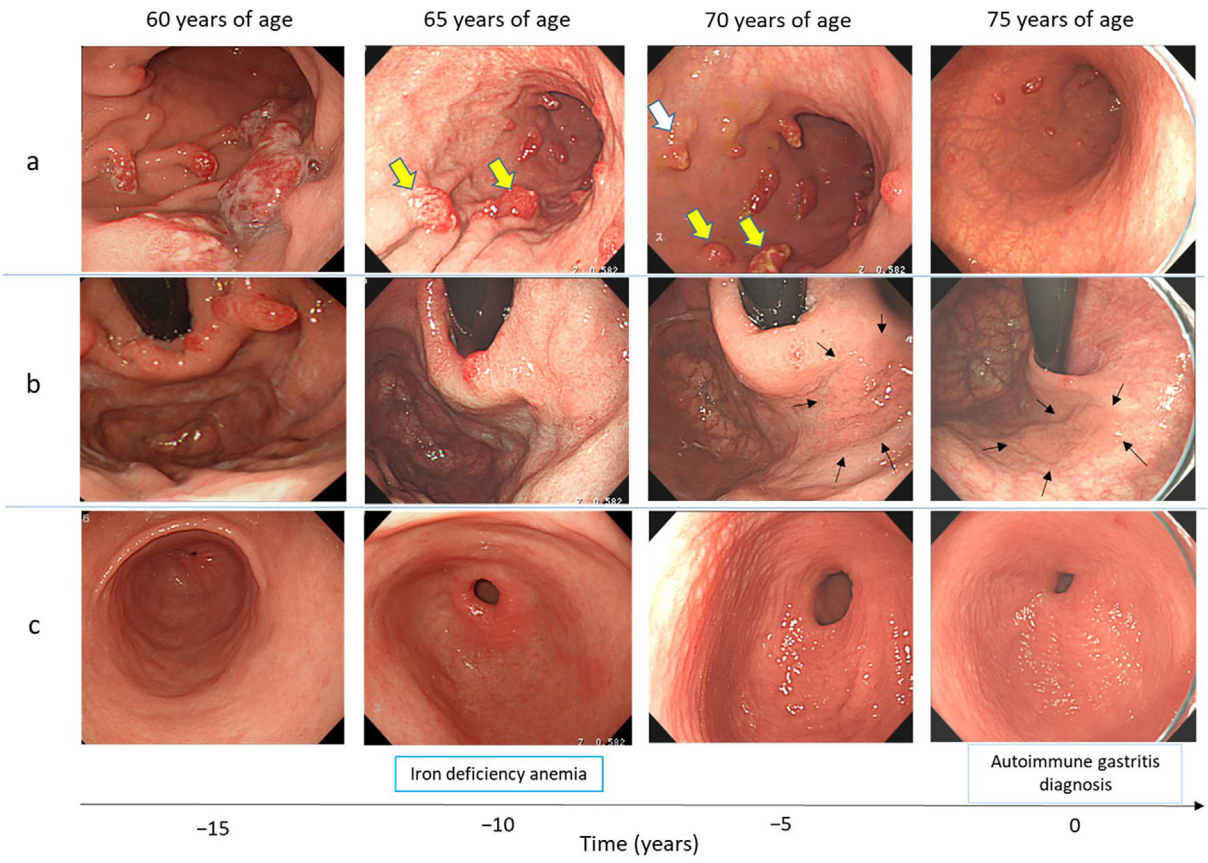

Figure 4. **Time course of endoscopic findings of Patient 2. a: Changes in the endoscopic image of the corpus. Some hyperplastic polyps had newly appeared (white arrows), and some had become smaller (yellow arrows); at the time of the diagnosis of autoimmune gastritis, fewer hyperplastic polyps were present, and they were smaller in size than on the previous images. b: Changes in the endoscopic image around the cardia. The hyperplastic polyps in the cardia had disappeared over time, and the remnant oxyntic mucosa (black arrows) had become clearly visible as the atrophy progressed. c: Changes in the endoscopic image of the antrum. A circular wrinkle-like pattern in the antral mucosa was observed from five years before the diagnosis of autoimmune gastritis.**

The other two patients had unexplained iron deficiency anemia over 10 years before the development of atrophic gastritis. Iron deficiency anemia in patients with AIG is often considered to be caused by impaired iron absorption due to achlorhydria associated with severe atrophic gastritis (12). However, Kulnigg-Dabsch et al. (13) reported that AIG may be present even in the absence of endoscopic atrophy and that serological and histological investigations are necessary. Because these patients had undergone no serological or histological investigations in the past, we were unable to determine whether AIG was already present at the onset of iron deficiency anemia. However, if AIG was a major contributor to the iron deficiency anemia in these patients, we would expect relapse of the iron deficiency anemia. A possible cause of the iron deficiency anemia in Patients 1 and 2 was hypothyroidism. Hypothyroidism can cause iron malabsorption or a decrease in iron incorporation, resulting in increased iron loss (14). Patients 1 and 2 were diagnosed with Hashimoto's thyroiditis at the same time as they developed iron deficiency anemia and were treated with combined iron and levothyroxine replacement.

Refractoriness to oral iron treatment is reportedly seen in about 70% of patients with AIG (15). Refractory anemia is defined as a poor response to oral iron therapy and failure of the hemoglobin level to increase by at least 1 g after 4 to 6 weeks of oral administration of 100 mg/day of elemental iron (16). The association between autoimmune thyroid disease and AIG is known as "thyrogastric syndrome," and about 40% of patients with AIG reportedly present with Hashimoto's thyroiditis (17). Because hypothyroidism causes iron malabsorption, patients with AIG who have iron deficiency anemia may need to be examined for hypothyroidism. In addition, patients with both hypothyroidism and iron deficiency anemia require treatment with a combination of iron and levothyroxine replacement (18). All patients with iron deficiency anemia who have no definite cause of blood loss may need to be examined for the possibility of AIG, hypothyroidism, or both.

In these three patients, the presence of gastritis had been recognized in the past, but the cause of the gastritis had not been identified, and the diagnosis of AIG became possible only after the atrophy had progressed to a predominance of

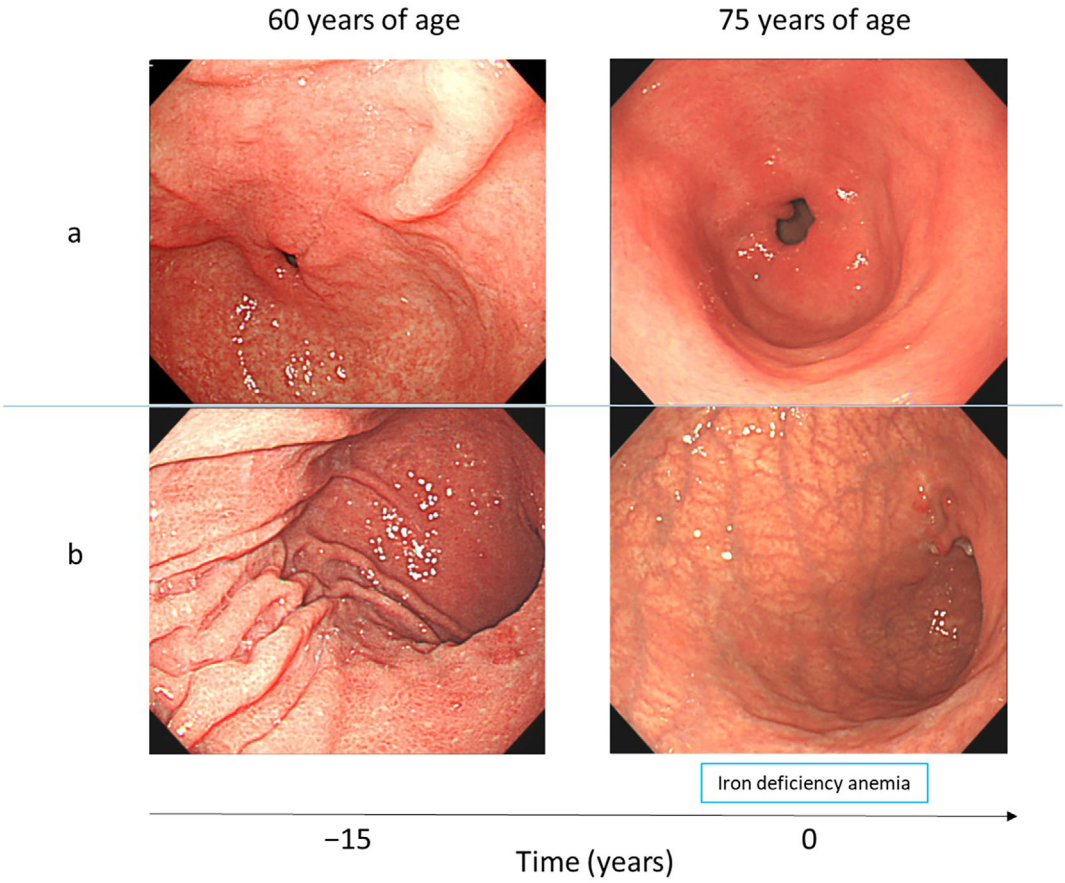

Figure 5. **Time course of endoscopic findings of Patient 3. a: Changes in endoscopic images of the antrum. There was no endoscopic evidence of gastritis in the antral mucosa on either image. b: Changes in the endoscopic image of the corpus. A previous image (at 60 years old) obtained 15 years before the diagnosis of autoimmune gastritis showed diffuse reddened and edematous mucosa without remarkable atrophic changes in the greater curvature.**

atrophic changes in the corpus. Two patients had unexplained iron deficiency anemia, but an additional examination for AIG was not carried out. Awareness of AIG will enable its accurate and timely diagnosis before the onset of typical clinical manifestations and severe atrophy.

In conclusion, endoscopic images of AIG vary widely depending on the stage of the disease progression. Therefore, it is important for clinicians not to be restricted by the concept of severe atrophic gastritis in the gastric body. AIG should be suspected when inflammatory changes are present in the mucosa of the gastric body due to hyperplastic polyps or swelling of the gastric area and when unexplained iron deficiency anemia is observed.

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

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