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【 CASE REPORT 】

Rapid Progression of Autoimmune Gastritis after *Helicobacter pylori* Eradication Therapy

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Abstract:
We herein report a case of autoimmune gastritis (AIG) with rapid progression after *Helicobacter pylori* eradication therapy. The patient's previous gastritis had followed the course of type B gastritis before eradication therapy for many years. Immediately after eradication, we diagnosed her with AIG and carefully followed changes in the endoscopic and histopathological findings and serum markers. All of these clinical findings showed significant atrophic progression in the corporal area for approximately three years. We concluded that *H. pylori* eradication therapy exacerbated AIG in this case.

Key words: autoimmune gastritis, *Helicobacter pylori*, eradication therapy, pepsinogen, atrophic gastritis, type B gastritis

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Introduction

The etiology of autoimmune gastritis (AIG) is still uncertain, and the relationship between *Helicobacter pylori* infection and AIG development also remains controversial. In Europe and the USA, many studies have suggested that *H. pylori*-infected gastritis may develop into AIG via a mechanism of cross-reactivity due to antigenic mimicry between *H. pylori* antigens and gastric proton pump (1, 2). This view is also supported by reports that the early stage of AIG can be healed by eradicating *H. pylori* (3) and that serum gastrin levels or prevalence of antigastric autoantibodies significantly decreased after *H. pylori* disappearance (4, 5). However, especially in Japan, the prevalence of AIG is very low, even though chronic *H. pylori* gastritis is a common disease. Furthermore, there are many reports of AIG cases found after *H. pylori* eradication (6, 7), and in some cases, it has been reported that reverse atrophy became obvious after eradication therapy, leading to a diagnosis of AIG (8, 9). These facts are also consistent with the result of an animal experimental study by Ohara et al., in which *H. pylori* infection suppressed the development of AIG (10).

Therefore, in *H. pylori*-infected AIG patients, it is necessary to carefully follow the changes before and after the eradication therapy and to evaluate the relationship on a case-by-case basis. However, in fact, it is very difficult to detect and diagnose pre-atrophic AIG during the course of ongoing *H. pylori* gastritis. To date, the only case report describing the course of *H. pylori*-infected AIG before and after the eradication therapy is that reported by Stolte et al. (11).

We herein report a case of *H. pylori*-infected AIG in which we were able to follow the histopathological changes and serological markers, including gastrin, pepsinogen (PG), and anti-parietal cell antibody (APCA), as well as endoscopic changes immediately after *H. pylori* eradication. To our knowledge, this is the first case report demonstrating rapid progression of AIG immediately after *H. pylori* eradication based on temporal changes in multiple clinical examinations.

Case Report

A 73-year-old woman had received regular treatment for hypertension and dyslipidemia and had undergone medical checkups for chronic gastritis at our clinic. She had a history of subclinical hypothyroidism caused by Hashimoto's

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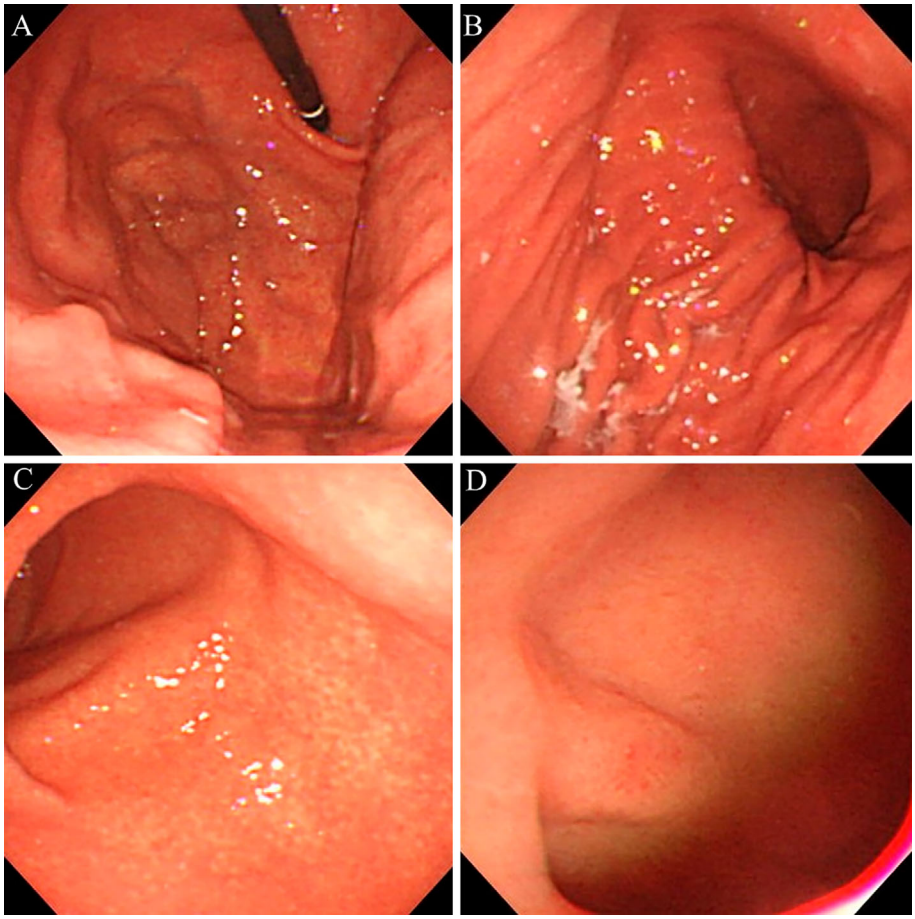

Figure 1. Endoscopic findings in 2008 (A-D). A, B: Atrophic changes did not extend to the upper corpus or the fornix. C: Small, round, yellowish-white nodules are observed in some parts of the greater curvature of the angular portion. D: Ulcer scarring in the anterior wall of the duodenal bulbus.

thyroiditis. She underwent her first upper gastrointestinal (UGI) endoscopy in 2008. At that time, the degree of atrophic change was C2 type according to the Kimura-Takemoto classification. In addition, endoscopy showed small nodular changes in the angular region and ulcer scarring in the anterior wall of the duodenal bulbus (Fig. 1). In February 2019, she complained of epigastric discomfort and underwent UGI endoscopy a second time. As a result, she was found to have *H. pylori* active gastritis with diffuse redness and atrophic changes corresponding to O2 type according to the Kimura-Takemoto classification (Fig. 2, 3).

The results of the *H. pylori* infection tests were as follows: the urea breath test (UBT) was positive at 3.7‰ (standard cut-off titer 2.5‰), and serum anti-*H. pylori* antibody was positive at 24 U/mL (E-plate EIKEN *H. pylori* Ab II, standard cut-off titer 10 U/mL). Serum PG I and PG II values were also measured for the evaluation of chronic gastritis and were abnormally high at 50.7 and 56.3 ng/mL, respectively.

The patient immediately received eradication therapy for *H. pylori*. Two months later, the result of the UBT indicated negative conversion to 0.4‰. At that time, the PG values were significantly reduced (Fig. 4); however, the PG II value was still high at 29.5 ng/mL. We also measured the serum gastrin level under a fasting condition, and it was abnormally elevated at 1,525 pg/mL (standard cut-off value, 200 pg/mL). She was not taking any acid-inhibitory agents, including proton-pump inhibitors, except for the eradication therapy. Due to a sign of hypergastrinemia and history of Hashimoto's thyroiditis, we measured the APCA titer, which was positive, with a high value of 1:1,280, whereas anti-intrinsic factor antibody (AIFA) was equivocal in the qualitative test.

We re-conducted UGI endoscopy in September 2019 because she was suspected of having AIG. The results of the histological examination were compatible with AIG, showing lymphocytic infiltration in the deeper part of the lamina propria mucosa and mild hyperplasia of enterochromaffin-like (ECL) cells (Fig. 5A, B). However, the degree of mucosal atrophy in the greater curvature of the corpus was mild to moderate with residual parietal cells. In addition, immunostaining for gastrin in the antral samples revealed no significant finding of G cell hyperplasia. On the other hand, the histological finding of active inflammation (neutrophilic infiltration) had already disappeared (Fig. 5A). The serum anti-*H. pylori* antibody level had also decreased to 8 U/mL.

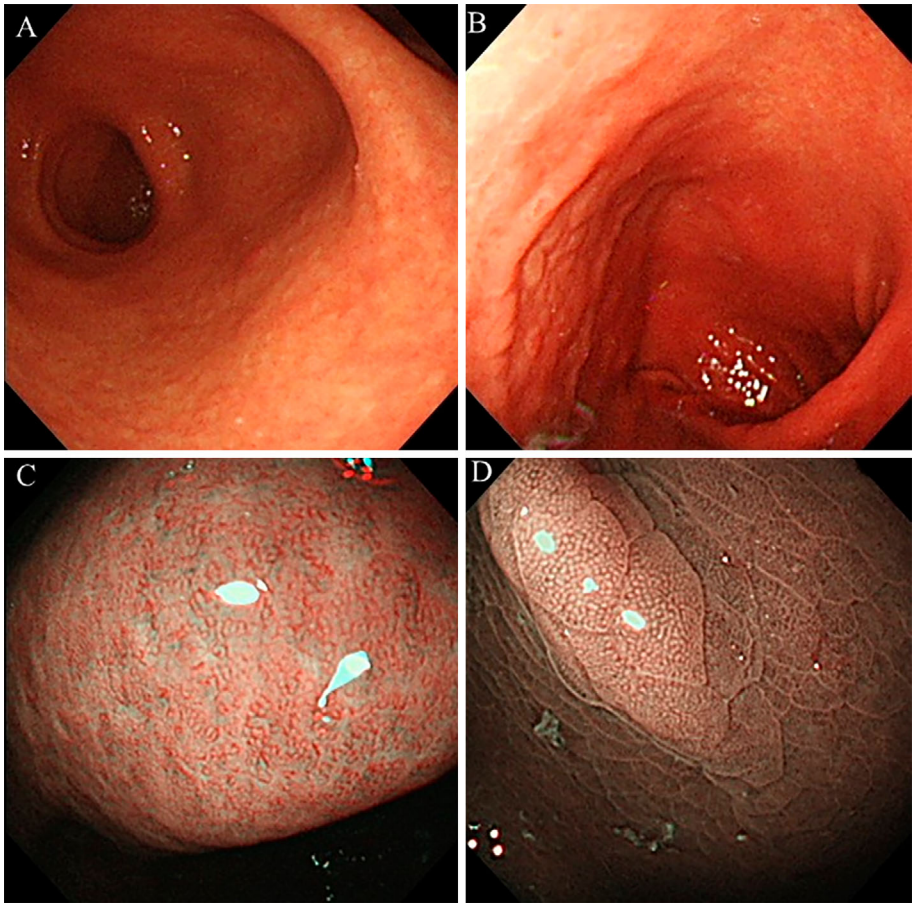

Figure 2. **Endoscopic findings just before the eradication therapy in Feb. 2019 (A-D). A: Image from the posterior side of the angular portion to the antrum. The coarse and fading mucosa continuously spreads from the antrum to the angular portion. B: Image from the upper corpus to the angular portion. The atrophic border lies on the anterior wall of the corpus. Diffuse redness is observed on the greater curvature side. C: Close-up image of the lesser curvature of the lower corpus by narrow-band imaging (NBI). The areae gastricae pattern is obscured, and the original gastric pits are lost with fading change. D: Close-up image of the greater curvature of the middle corpus by NBI. The areae gastricae pattern is clear and regular with no intervening parts, and the original gastric pits are preserved in an orderly manner.**

Subsequently, we followed the serum markers of PG I, PG II, gastrin, and APCA on regular blood tests. The values of PG I continued to show a further decreasing trend, whereas the other markers showed no significant changes, remaining high (Fig. 4). The PG II values also continued to remain high at >20 ng/mL.

Endoscopy was next performed in July 2020. In this examination, remarkable progression of atrophic change was observed, showing discolored changes and marked vascular visibility in the corporal mucosa (Fig. 3). The atrophic changes encompassed the entire area of the corpus, corresponding to the so-called O4 (Op) type. A histological examination of three biopsy specimens obtained from the greater curvature of the corpus (upper: 1, middle: 1, and lower: 1) showed lymphocytic infiltration in the deeper part of the lamina propria mucosa and mucous cell metaplasia. However, the density of the oxyntic glands remained, and many parietal cells exhibited pseudohypertrophic changes with 'snouting' (luminal cytoplasmic projections) in some areas (Fig. 5C).

Endoscopy performed in August 2021 showed more severe atrophic changes with faded colors in most areas of the corpus (Fig. 3). A histopathological examination of four biopsy specimens obtained from the greater curvature of the corpus (upper: 2, middle: 1, and lower: 1) revealed remarkably advanced atrophic changes (Fig. 5E). The glandular structure in the oxyntic mucosa became more non-uniform, mostly with pyloric metaplasia (PG I staining: negative) rather than pseudopyloric metaplasia (PG I staining: positive). In addition, chief and parietal cells were not as clearly recognized as they had been previously, and ECL cell hyperplasia was more advanced than at the previous endoscopic examinations (Fig. 5B, D, F). The temporal changes in the updated Sydney classification corresponding to Fig. 5 are summarized in Table 1.

The results of her blood tests in 2019, including serological biomarkers of other autoimmune diseases, are shown in Table 2. Although she seemed to have congenital autoim-

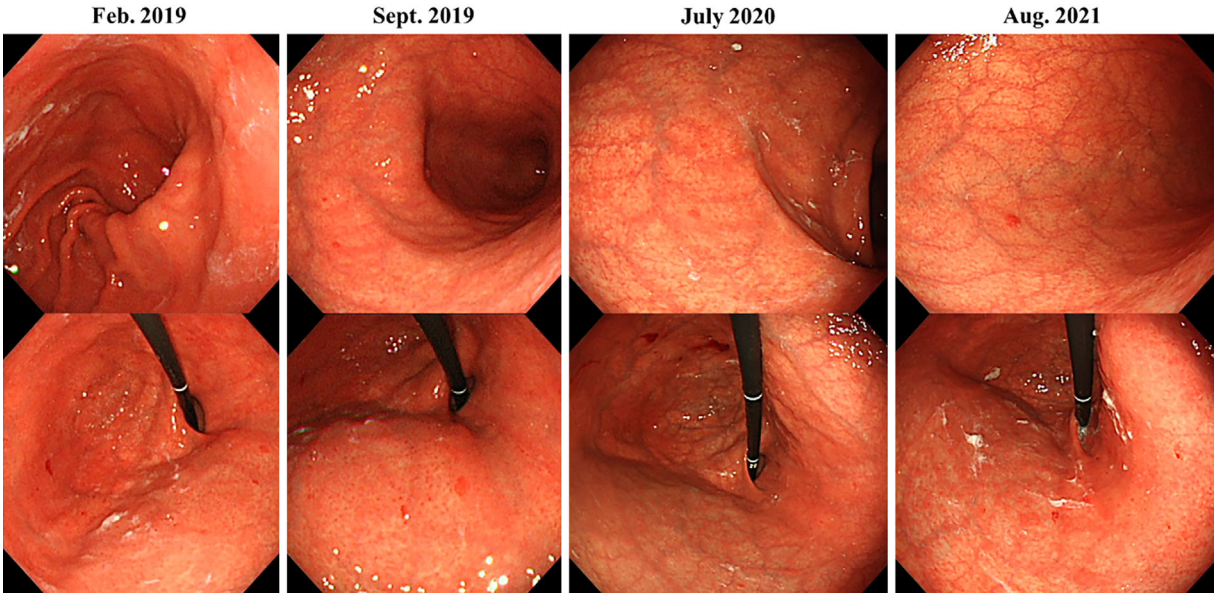

Figure 3. **Temporal changes in endoscopic findings before and after the eradication therapy. Significant progression of atrophic changes was observed in the corpus, especially in the greater curvature side. Small hyperplastic polyps and lesions were observed in some areas.**

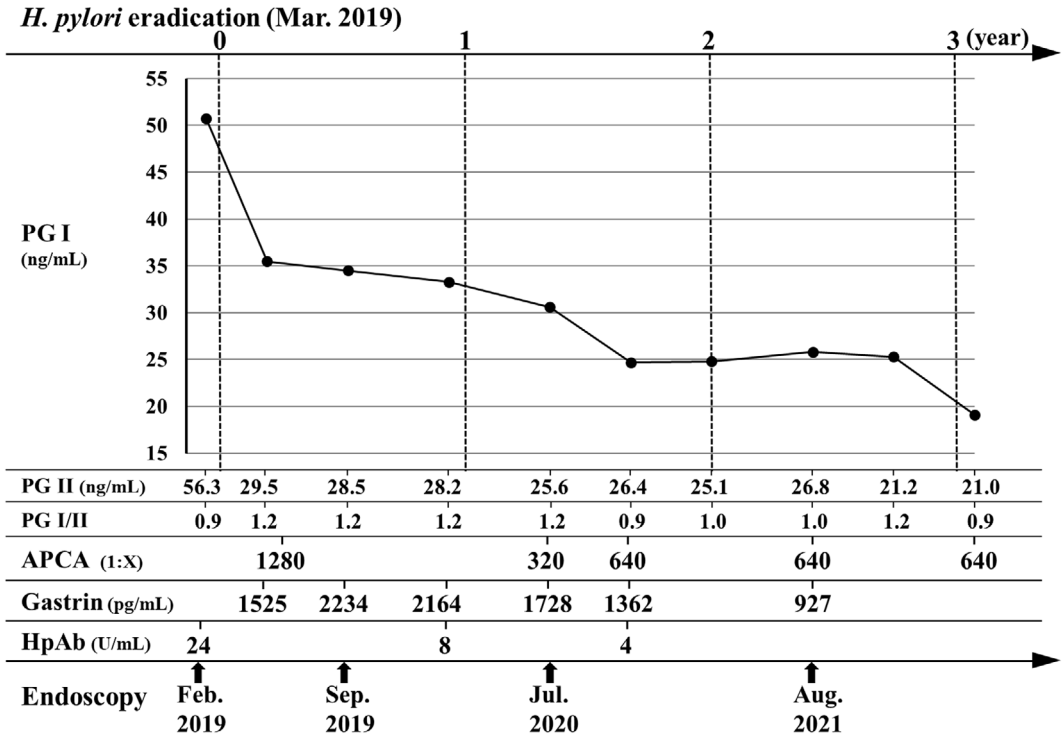

Figure 4. **Time course of serum markers before and after *H. pylori* eradication. APCA: anti-parietal cell antibody, HpAb: serum anti-*H. pylori* antibody, PG I: pepsinogen I**

mune factors, she was asymptomatic and in a euthyroid state without any specific therapy. In addition, no findings of iron deficiency anemia or pernicious anemia have been found in her regular blood tests until now.

All procedures were performed in accordance with the ethical standards of the 1964 Declaration of Helsinki and its later amendments. Informed consent was obtained from the patient.

Discussion

Regarding the association between *H. pylori* infection and AIG, many reports from Europe and the USA suggest that *H. pylori* infection is involved in the development of

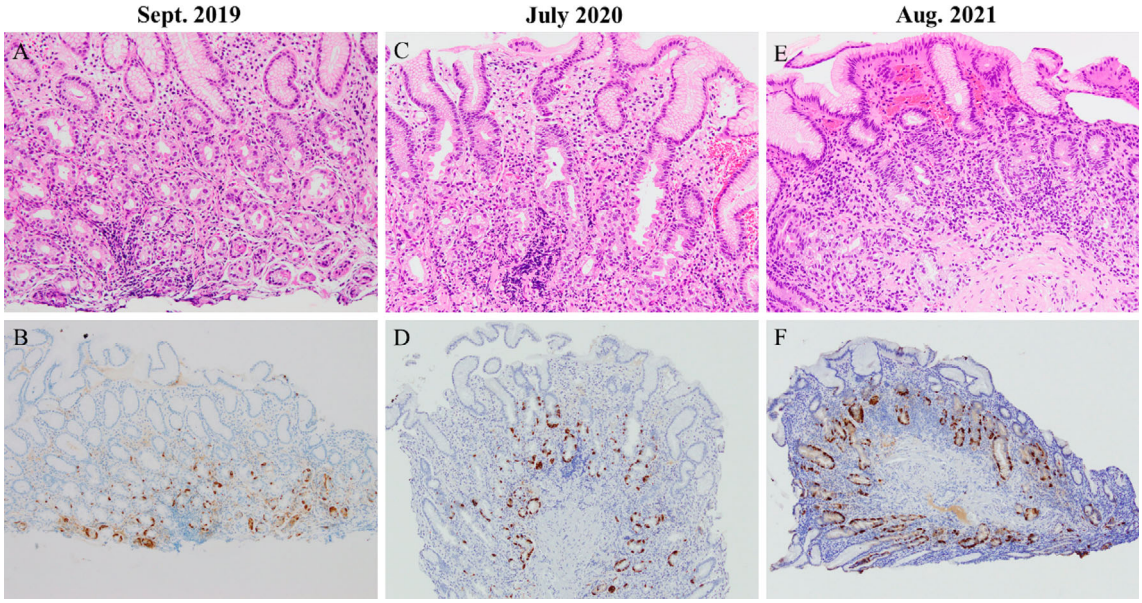

Figure 5. Histopathological findings in 2019 (A, B), 2020 (C, D), and 2021 (E, F). A, C, E: Biopsy specimens obtained from the greater curvature of the upper corpus (Hematoxylin and Eosin staining, original magnification ×200). B, D, F: The same specimens as in A, C, and E, respectively (immunohistochemical staining for chromogranin A, original magnification ×100).

Table 1. Temporal Changes in the Updated Sydney Classification.

	Sept. 2019	July 2020	Aug. 2021
Mononuclear cell infiltration	Moderate	Moderate	Severe
Neutrophil infiltration	None	None	None
Glandular atrophy	Mild	Moderate	Severe
Intestinal metaplasia	None	None	None
H. pylori	None	None	None

Histological assessment of biopsy specimens obtained from the greater curvature of the upper corpus.

AIG (1, 2, 12). In fact, many AIG cases have been reported to show signs of previous *H. pylori* infection (4, 13-15). However, only a limited number of reports have shown improvement in AIG after *H. pylori* eradication therapy (3, 4, 11). To date, the only case report is that of Stolte et al., who described a 22-year-old man diagnosed with AIG based on histopathological findings of focal destruction of the oxyntic glands by lymphocytic infiltration and parietal cell pseudohypertrophy (11). The histological findings in that case had reportedly improved by 15 months after *H. pylori* eradication therapy. However, in this case, despite being diagnosed with AIG, the elevation of the gastrin level was reportedly slight, and both the APCA and AIFA were negative.

In this present case, there were prerequisite data to evaluate the progression of AIG accurately after *H. pylori* eradication. First, the diagnosis of current *H. pylori* infection before the eradication therapy was based on the serological and endoscopic findings (Fig. 2-4), neither of which was dependent on the urease activity. The disappearance of *H. pylori* was also confirmed by a significant decrease in the serum antibody titer (Fig. 4) and the histological findings (Fig. 5, Table 1). Second, at the time of *H. pylori* eradication, atrophic changes in the corporal area had not progressed extensively, and the oxyntic glands had relatively remained. Third, we were able to notice the development of AIG immediately after performing eradication therapy. Two months after eradication, the serum gastrin level indicated a state of marked hypergastrinemia. In addition, the APCA titer was positive, showing a high level of 1,280-fold, which led to the final diagnosis of AIG along with the histological findings.

Surprisingly, in our case, the changes after the eradication showed a course in contrast to the case reported by Stolte et al. (11). The endoscopic examinations performed at 6, 16, and 29 months after the eradication showed obvious progression of atrophic changes in the corporal area (Fig. 3). Similarly, the histological examinations also revealed obvious progression of atrophic changes in the oxyntic glands with the enhancement of massive ECL hyperplasia (Fig. 5, Table 1). In addition, the PG I values showed a significant decrease over approximately three years after eradication

Table 2. Laboratory Blood Test Findings.

Complete blood cell counts		Reference range	Thyroid function		Reference range
WBC (×10²/μL)	58	(35-91)	TSH (μIU/mL)	1.15	(0.54-4.54)
RBC (×10⁴/μL)	434	(376-500)	Free T3 (pg/mL)	3	(2.1-4.2)
Hb (g/dL)	14.0	(11.3-15.2)	Free T4 (ng/dL)	1.25	(0.97-1.72)
Ht (%)	41.9	(33.4-44.9)			
MCV (fL)	96.5	(79.0-100.0)	**Immunological test**		**Reference range**
MCHC (%)	33.4	(30.7-36.6)	IgG (mg/dL)	1,788	(870-1,700)
Platelets (×10⁴/μL)	14.5	(13.0-36.9)	IgA (mg/dL)	152	(110-410)
			IgM (mg/dL)	277	(46-260)
Biochemistry		**Reference range**	Anti TSH-R Ab (IU/L)	<0.8	(<2.0)
TP (g/dL)	7.6	(6.5-8.3)	Anti Tg Ab (IU/mL)	462	(<28)
AST (U/L)	27	(8-38)	Anti TPO Ab (IU/mL)	176	(<16)
ALT (U/L)	21	(4-43)	ANA	1:1280	(<40)
LDH (U/L)	200	(121-245)	Anti ss-DNA Ab (U/mL)	7.7	(<7.0)
γGTP (U/L)	31	(<48)	Anti ds-DNA Ab (IU/mL)	4.9	(<10.0)
Creatinine (mg/dL)	0.66	(0.47-0.79)	Anti centromere Ab (U/mL)	240	(<7.0)
LDL-C (mg/dL)	146	(70-139)	Anti SS-A Ab (U/mL)	4.9	(<7.0)
HDL-C (mg/dL)	77	(40-90)	Anti SS-B Ab (U/mL)	4.9	(<7.0)
Triglycerides (mg/dL)	54	(30-149)	Anti GAD Ab (U/mL)	<5.0	(<5.0)
Glucose (mg/dL)	80	(60-109)	RF (IU/mL)	<4	(<15)
HbA1c (%)	5.3	(4.6-6.2)	C3 (mg/dL)	108	(65-135)
Na (mEq/L)	144	(135-150)	C4 (mg/dL)	25	(13-35)
K (mEq/L)	4.2	(3.5-5.3)	CH50 (CH50/mL)	41.7	(30.0-46.0)
Fe (μg/dL)	65	(48-170)			
Ferritin (ng/mL)	39	(5-152)			
Vitamin B12 (pg/mL)	721	(233-914)			
CRP (mg/dL)	0.09	(<0.30)			

Underlined items and values indicate outliers. WBC: white blood cells, RBC: red blood cells, Hb: hemoglobin, Ht: hematocrit, MCV: mean corpuscular volume, MCHC: mean corpuscular hemoglobin concentration, TP: toral protein, AST: aspartate aminotransferase, ALT: alanine aminotransferase, LDH: lactate dehydrogenase, γGTP: γ-glutamyltransferase, LDL-C: low-density lipoprotein cholesterol, HDL-C: high-density lipoprotein cholesterol, CRP: C-reactive protein, TSH: thyroid-stimulating hormone, Ig: immunoglobulin, TSH-R: TSH receptor, Ab: antibody, Tg: thyroglobulin, TPO: thyroid peroxidase, ANA: antinuclear antibody, ss-DNA: single stranded DNA, ds-DNA: double stranded DNA, SS: Sjögren's syndrome, GAD: glutamic acid decarboxylase, RF: rheumatoid factor

(Fig. 4). The serum PG level reflects the gastric mucosal inflammatory status and the severity of atrophic gastritis (16). This rapid decrease in the PG I values is thought to indicate the marked progression of atrophic changes in the oxyntic gland area. In contrast, the PG I/II ratios remained almost the same until the latest examination (Fig. 4). Usually in type B gastritis, the PG I/II level gradually recovers after *H. pylori* eradication. These ratios in our case are considered to be due to the PG II values remaining high, which is considered to indicate the persistence of active inflammation due to AIG. Similarly, the serum gastrin values continued to be extremely high (Fig. 4), although these values tend to normalize as the oxyntic mucosa recovers after eradication therapy. Based on these findings, acute exacerbation of AIG after the eradication was unquestionable in this case.

Unfortunately, we did not measure the serological markers or perform histological evaluations before the eradication therapy. In addition, previously obtained endoscopic images did not clearly show characteristic findings of early AIG, such as pseudopolyposis. Therefore, whether mild AIG, which can be confirmed histologically, had already developed before the eradication or whether immunological attack due to AIG began in earnest after the eradication is unknown. However, it has been pointed out that asymptomatic AIG, a chronic inflammatory disease, precedes the onset of corpus atrophy by 10-20 years (17). This suggests that it was unlikely that AIG developed with a sudden outbreak only in recent years. Furthermore, the APCA level immediately after eradication was very high at 1:1,280, and it is hard to imagine that the autoimmune abnormalities suddenly started after eradication. Either way, the development of AIG in our case was very slow or late compared to the mean age, serum PG I level, and endoscopic atrophic grade reported in a large-scale Japanese survey (18) and an analysis targeting a health checkup service (7). In addition, a histological examination just after the eradication showed findings compatible with early-stage AIG.

However, before the eradication therapy, the patient's gastritis had shown the pattern of *H. pylori* gastritis (type B gastritis) for a long time (Fig. 1). Even in 2019, the endoscopic images retained the pattern of type B gastritis and did not show features of typical AIG with reverse atrophy (Fig. 2). This course is inconsistent with the results of long-term retrospective observations of pure AIG cases reported

by Ayaki et al (19).

Given these findings, we suspect that the preceding *H. pylori* gastritis may have suppressed the AIG activity or delayed its onset until after eradication therapy. This view is supported by the results of the animal study by Ohara et al. (10). In addition, our case had high titers of autoantibodies for Hashimoto's disease and systemic sclerosis, the genetic factors of which are closely related to those of AIG (Fig. 2) (20, 21). The high activity of AIG after the eradication may have been evoked by the congenital potential of these autoimmune predispositions.

We concluded that this was a case of AIG exacerbation after *H. pylori* eradication. Although only one case was presented in this report, we believe that our case provides evidence for an interaction between *H. pylori* gastritis and AIG and that the interaction was a suppressive relationship. There may be many more similar cases where AIG remains inconspicuous under *H. pylori* active gastritis and is rapidly exacerbated after *H. pylori* eradication therapy. To solve this problem, we need to pay attention to not only typical AIG cases with advanced reverse atrophy but also atypical AIG cases concealed by *H. pylori* gastritis.

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

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