Prevalence and Clinical Characteristics of Autoimmune Gastritis in Patients with Severe Atrophic Gastritis

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Abstract

Objective: Recent reports indicate that the prevalence of Autoimmune Gastritis (AIG) is increasing among patients with atrophic gastritis. The aim of our study was to investigate the prevalence and clinical characteristics of AIG in patients with Severe Atrophic Gastritis (SAG).

Methods: Endoscopic mucosal atrophy was evaluated using the Kimura-Takemoto classification. AIG was defined as 1) endoscopic SAG of the corpus, 2) hypergastrinemia (≥ 250 pg/mL), and 3) presence of anti-parietal cell antibody (PCA) (titer ≥ 20-fold) or intrinsic factor antibody (IFA). Anti- H. pylori IgG antibody, gastrin, and pepsinogen levels were also determined.

Patients: We prospectively enrolled 30 patients (19 men, mean age 62.5 years) with endoscopic SAG who underwent gastrointestinal endoscopy.

Results: AIG was diagnosed in 3 out of 30 cases (10.0%) (Kimura-Takemoto classification: O-III: 22.2% [2/9] and O-II: 4.8% [1/21]). In the 3 AIG cases, the positivity rates were 100%, 33.3%, and 33.3% for PCA, IFA expression, and H. pylori infection, respectively. The mean gastrin level was significantly higher in the AIG group than in the non-AIG group (1064.7 ± 456.6 pg/mL vs. 147.6 ± 28.9 pg/mL, p<0.0001), whereas the mean pepsinogen I/II ratio was significantly lower in the AIG group (0.87 ± 0.22 vs. 3.75 ± 0.23, p=0.0003).

Conclusion: Endoscopic examiners should consider the presence of AIG in patients with SAG. The titer of PCA and serum levels of gastrin and pepsinogen I/II ratio are useful diagnostic markers of AIG. This study was registered as UMIN000032192.

Keywords: Autoimmune gastritis; Atrophy; Endoscopy; H. pylori infection

Introduction

Autoimmune Gastritis (AIG) is a subtype of chronic gastritis in which gastric parietal cells are destroyed by the production of auto antibodies against the proton pump located in parietal cells [1]. Both inflammation and atrophy are restricted to the corpus, not to the antrum, because parietal cells are located in the corpus and fundus glands.

Parietal cells produce hydrochloric acid and an intrinsic factor, and total loss of these cells causes iron deficiency anemia and Pernicious Anemia (PA). This phenomenon also leads to hypergastrinemia and causes hyperplasia of enterochromaffin-like cells, resulting in complications such as hyperplastic polyps, gastric cancer, and Neuroendocrine Tumors (NET) [2-8]. In addition, AIG has been reported to be highly associated with autoimmune diseases of extra-stomach glandular tissues such as the thyroid gland and pancreas gland and with a high incidence of malignant tumors in other organs [9-13]. Therefore, AIG is a gastric disease but should be recognized as a systemic disorder [14,15].

AIG is considered to be a common disease in Northern Europe and especially in Scandinavia, where it is associated to a high frequency of PA; however, it is a rare disease in Japan, where the frequency of PA is very low [16]. In a previous Japanese study, Sugihara et al. [17] showed that the...
estimated prevalence of PA caused by AIG was 0.34 to 0.5 per 100,000 people.

In recent years, gastroenterologists focused their attention on AIG, and it became clear that it is not a rare disease in Japan, mainly through characteristic incidental findings (corpus-predominant atrophy and coexistence with multiple hyperplastic polyps) during endoscopic cancer screenings, when patients with severe atrophic gastritis, autoimmune diseases and refractory cases of H. pylori eradication undergo endoscopy [18-21].

Therefore, AIG may have been clinically under diagnosed; therefore, we hypothesized that it was more frequent than was commonly believed in patients with Severe Atrophic Gastritis (SAG) in Japan. The prevalence of AIG in patients with SAG remains unknown, and the aim of our study was to investigate its prevalence and clinical characteristics in these patients.

Methods

Study population

Subjects were individuals who visited the General Health Promotion Center, Kawasaki Medical School General Medical Center, for a detailed medical check-up examination to know their health between August 2018 and March 2019. Patients who underwent endoscopy and blood chemistry examination between the ages of 20 to 79, regardless of gender were included for registration.

During the study period, a total of 517 subjects (319 men, 198 women; mean age 51.6 years, range 22 to 78 years) underwent blood chemistry examination and routine upper gastrointestinal endoscopy. A precise medical history, including present and past illnesses (for example thyroid disease), history of taking medicine (acid suppressive drugs), and presence or absence of eradication therapy, was obtained in an interview with the patient conducted by a public health nurse. Concomitant diseases were screened from patients’ medical history and additional laboratory examinations.

After endoscopy, we prospectively and consecutively registered patients with endoscopically diagnosed SAG who provided informed consent. Exclusion criteria were the use of antacids, H2-receptor antagonists, or proton pump inhibitors; a history of gastric surgery; and systemic diseases such as renal failure.

Endoscopy

Endoscopy was performed by certified Endoscopists using an Olympus video scope (GIF-HQ290, Olympus, Tokyo, Japan) or a FUJIFILM one (EG-L580NW7, FUJIFILM Co., Ltd., Tokyo, Japan) at our hospital. The endoscopists diagnosed the presence of organic lesions such as gastric cancer and evaluated mucosal atrophy using the Kimura-Takemoto classification [22]. This classification is used to divide gastric mucosal atrophy into six grades (C-I, C-II, C-III, O-I, O-II, and O-III) based on endoscopic assessment of the extent of the atrophic border. C-I and C-II are defined as mild, C-III and O-I as moderate, and O-II and O-III as severe atrophy.

The same certified endoscopists independently evaluated the grade of atrophy, the presence of specific endoscopic findings (corpus-dominant atrophy; disappearance of gastric folds; remnant oxyntic mucosa; sticky adherent dense mucus; xanthoma) and other comprehensive findings such as cancer, adenoma, hyperplastic polyps, and NET from all patients enrolled in this study. They were affiliated to the same Medical Center as the authors, and consensus was reached after discussion, in cases of discrepancy.

Serology

Serum samples were obtained from SAG patients and stored at -80°C, then concentrations of anti-Parietal Cell Antibody (PCA), anti-Intrinsic Factor Antibody (IFA), anti- H. pylori IgG antibody (E-plate, Eiken Chemical Co., Ltd., Tokyo, Japan), gastrin, and Pepsinogen (PG) were determined. PCA was evaluated utilizing a fluorescent antibody test in which a patient’s serum is diluted 10-fold and visually determined using the stomach of a rat. Gastrin was measured using radioimmunoassay with polyethylene glycol, and IFA and PG using Chemiluminescence Enzyme Immunoassay (CLEIA).

Diagnostic criteria

In this study, a positive finding for PCA (standard cut-off titer: 10-fold) was defined as a titer ≥ 20-fold to reduce false-positives, and a fasting gastrin level of ≥ 250 pg/mL was considered as indicating hypergastrinemia, according to our previous study [23]. The E-Plate EIKEN H. pylori IgG antibody has a standard cut-off titer of 10 U/mL, but we defined the cut-off value as 3 U/mL to reduce false negatives. The status of H. pylori infection was determined based on the medical history and results of serum anti- H. pylori IgG antibody test.

AIG was defined as 1) endoscopic SAG of the corpus, 2) hypergastrinemia (≥ 250 pg/mL), and 3) presence of PCA (titer ≥ 20-fold) or IFA. The presence of all the above three criteria was a must for diagnosis of AIG.

Outcome measurement

We investigated the prevalence of AIG in patients with SAG and compared the clinical, serological, and endoscopic features between the AIG and non-AIG groups. We defined the non-AIG group as patients who did not meet the criteria for AIG in those with SAG.

Statistical analyses

Continuous variables at baseline are expressed as mean with standard error. Categorical variables at baseline are expressed as frequency. Continuous variables included the age, serum gastrin, serum PG I, PG II, PG I/II ratio, and hemoglobin levels. Categorical variables included gender, presence of thyroid disease, Kimura-Takemoto classification, PCA, IFA and H. pylori status, and endoscopic features. Comparisons between two groups were performed using the Student’s t-test for continuous variables and the Fisher’s exact test for categorical variables. P-values <0.05 were considered statistically significant. All analyses were performed using Prism software version 8 (GraphPad Software Inc., La Jolla, CA, USA).

Results

Prevalence of AIG, and comparison of clinical characteristics between the AIG and non-AIG groups

During the study period, we enrolled 30 patients (19 men and 11 women; age range, 43 to 85 years; mean age, 62.5 years) with endoscopically diagnosed SAG. Three of the 30 patients (two men, mean age 68.0 years) met the diagnostic criteria of AIG, while the other 27 were included in the non-AIG group (17 men, mean age 61.9 years). The prevalence of AIG in SAG was thus 10.0% (3/30).

Table 1 shows the comparison of clinical and serological characteristics between the AIG and non-AIG groups. Medical interviews revealed that two of the AIG cases had thyroid disease (one case of hyperthyroidism and one of hypothyroidism); while none of the non-AIG patients had thyroid disease. Distribution of the Kimura-Takemoto classification was O-III in 30.0% of patients (9/30) and O-II in 70.0% (21/30). When comparing this classification between...
the two groups, the prevalence of AIG was higher in O-III cases than in O-II cases, but the difference was not significant (22.2% vs. 4.8%, p=0.21). In the three patients with AIG, the positivity rates were 100% (titer >20-fold in all patients), 33.3%, and 33.3% for PCA, IFA expression, and \textit{H. pylori} infection, respectively. On the other hand, in the non-AIG group, PCA expression was titer <10-fold in 74.1% of patients and between 10-fold in 25.9%; no patients in this group showed titer >20-fold. IFA expression was not found in this group, and the \textit{H. pylori} status was negative in 1 patient, positive in 5, and eradicated in 21.

The mean serum gastrin level was significantly higher in the AIG group than in the non-AIG group (1064.7 ± 456.6 pg/mL [range, 440 to 1954] vs. 147.6 ± 28.9 pg/mL [range, 53 to 870], p<0.001). In addition, the mean serum PG I/II ratio was significantly lower in the AIG group than in the non-AIG group (0.87 ± 0.22 [range, 0.6 to 1.3] vs. 3.75 ± 0.23 [range, 1.3 to 5.4], p=0.0003). The mean serum hemoglobin concentration was not significantly different between the two groups (15.4 ± 0.47 [range, 14.5 to 16.1] vs. 14.3 ± 0.29 [range, 11.5 to 17.6], p=0.22).

**Comparison of endoscopic features between the AIG and non-AIG groups**

The prevalence of corpus-predominant atrophy was significantly higher in the AIG group than in the non-AIG group (66.7% vs. 0%, p=0.007; Table 2), as in only 1 patient with AIG, corpus-predominant atrophy was not seen clearly. Both disappearance of gastric folds and hyperplastic polyps were more common in the AIG group than in the non-AIG group, but no statistically significant difference was found. Remnant oxyntic mucosa and sticky adherent dense mucus were seen in only 1 patient with AIG, while none of the non-AIG patients had either finding. On the other hand, gastric xanthoma was seen only in the non-AIG group (5/27, 18.5%; Table 2).

**Anti-gastric antibody, serological markers, and endoscopic features in patients with AIG**

Table 3 shows detailed data on anti-gastric antibody, serum gastrin and PG concentration, titer of \textit{H. pylori} antibody, and endoscopic features in the 3 patients with AIG.

Case 1 was positive for \textit{H. pylori} (titer 29 U/mL), and both PG I and II values were remarkably higher than in cases 2 and 3. In addition, because gastric atrophy was observed not only in the corpus but also in the antrum, findings of corpus-dominant atrophy were not evident. In this case, AIG was concomitant with gastric hyperplastic polyps.

Case 2 was negative for \textit{H. pylori} (titer <3 U/mL), and hypergastrinemia (440 pg/mL) as well as low PG I and PG I/II ratio were found together with corpus-dominant atrophy, disappearance of gastric folds, remnant oxyntic mucosa, and sticky adherent dense

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**Figure 1:** A case of early gastric cancer with AIG.

This case was an 83-year-old female with a history of hypothyroidism. GI endoscopy revealed an irregular depressive lesion (type O-IIa) in the posterior wall of the lower corpus (a). Two small hyperplastic polyps were also observed in the corpus (b). Remarkably visible vessels of the gastric mucosa and the disappearance of gastric folds (Kimura-Takemoto Classification: O-III) were seen in the greater curvature of the corpus (c), whereas no atrophic change was seen in the antrum (d) (corpus-dominant atrophy). The gastric tumor was resected via subtotal gastrectomy. Cancer cells with mucin production in combination with signet ring cell carcinoma are seen in the gastric mucosa spreading to the submucosa (hematoxylin-eosin: HE, 10×4) (e). Infiltration of lymphocytic cells predominates in the deep mucosa of the fundic gland region, resulting in the destruction and disappearance of parietal cells (HE, 20×10) (f). In the pyloric gland region, no mucosal atrophy is observed (HE, 20×10) (g). Chromogranin A staining of atrophic mucosa. The black arrow indicates Endocrine Cell Micronests (ECMs) positive for chromogranin A (chromogranin A, 20×10) (h).

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**Table 1:** Comparison of clinical characteristics and serological features between the AIG and non-AIG groups.
mucus. AIG was concomitant with gastric adenoma.

Case 3 was also negative for *H. pylori* (titer <3 U/mL), had remarkable hypergastrinemia (1,954 pg/mL), and extremely low PG I and PG I/II ratio, together with corpus-dominant atrophy. AIG was concomitant with gastric cancer and hyperplastic polyp.

A representative case of gastric cancer with AIG is shown in Figure 1 (case 3).

The final pathological assessment after resection of the stomach revealed a gastric tumor of 27 mm × 18 mm, M (less-post), O-IIc + IIa, sig>muc>por 2, pT1b SM2, Ly0, v1, N0, p Stage IA. Histological findings were consistent with AIG.

Clinical and endoscopic characteristics of PCA 10-fold patients in the non-AIG group

In this study, having defined the PCA titer positivity cut-off as ≥20-fold for AIG diagnosis, cases of 10-fold PCA titer were not diagnosed as AIG. Table 4 shows clinical and endoscopic characteristics of the 7 patients with PCA 10-fold in the non-AIG group. None of these patients had hypergastrinemia (mean 150.8 ± 18.6 pg/mL; range: 96 to 240). The mean PG I concentration and mean I/II ratio were 22.3 ± 4.3 ng/mL (range: 14.6 to 44.4) and 4.0 ± 0.4 (range: 2.6 to 5.4), respectively. In endoscopic findings, disappearance of gastric folds was found in 3 out of 7 patients, but none had corpus-dominant atrophy, hyperplastic polyp, remnant oxyntic mucosa, or sticky adherent dense mucus.

**Discussion**

In our prospective study, the prevalence of AIG in patients with SAG was 10% (O-III: 22.2%; O-II: 4.8%). These data demonstrate that AIG is not, as previously thought, a rare disease, as this frequency is higher than that reported previously. Recently, Aoki et al. [24], in a retrospective study of 8,761 patients enrolled at 5 institutions who underwent endoscopic screening, reported that the prevalence of AIG in the general population of Japan was 0.49% for adults, 0.9% for women, 0.14% for men, and 6.22% for severe atrophy patients. In addition, Notsu et al. [18] showed that among 6,739 Japanese subjects who underwent health checkup examination, 33 were diagnosed with AIG based on the endoscopic findings, for an overall prevalence of 0.49% (women 0.65%, men 0.40%). In China, Zhang et al. [25] indicated that based on 320 patients with AIG, the annual detection rate was 0.9%, so that AIG was more frequent than expected. Our prospective study could not measure the prevalence of AIG in the general population but estimated the prevalence in SAG patients. However, we believe that a large-scale research effort in the future is necessary to accurately measure such prevalence, as our sample size was small. In addition, future studies with involvement of more medical centers in Japan and possibly other Asian countries are warranted for establishing reliability of the results of this study.

In our 3 patients with AIG, only 1 (case 1) showed seropositive of *H. pylori* infection. Two contrasting accounts of the relationship between the development of AIG and *H. pylori* infection have been proposed. One theory maintains that *H. pylori* can activate gastric CD4+ Th1 cells that recognize cross-reactive epitopes shared by *H. pylori* proteins and self H+, K+ - ATPase, leading to gastric autoimmunity [26,27]; the other posits that *H. pylori* infection changes the microenvironment of the gastric mucosa by inducing
a Th2 immune response in addition to a Th1 response, leading to regression of autoimmune gastritis [28,29]. Unfortunately, any immunological testing for Th1 and Th2 responses was not performed in this study. Our previous reports by Haruma et al. [16] and Saito et al. [30] showed that in Japanese cases with PA, no cases of H. pylori infection were found. We hypothesize that the recent, dramatically rapid decrease in the prevalence of H. pylori infection following the improvement of sanitation in Japan might have contributed to the gradual increase in patients with AIG [31].

Hypergastrinemia caused by gastric hypochlorhydria and low levels of serum PG I and of the PG I/II ratio have been reported in patients with AIG [8,16,18-20]. In our study, serum gastrin level was significantly higher and the PG I/II ratio significantly lower in the AIG group than in the non-AIG group, as previously reported. However, serum PG I showed no difference between the two groups, because case 1 was positive for H. pylori infection. Notsu et al. [18] showed that serum gastrin and PG I/II ratio are inversely correlated. Case 3, with gastric cancer, showed remarkable hypergastrinemia and extremely low PG I/II ratio. In addition, Case 2, with gastric adenoma, also showed hypergastrinemia and extremely low PG I/II ratio. Our previous study showed that serum gastrin levels were significantly higher in patients with gastric cancer than in controls and can cause severe morphological changes in gastric cancer through the gastrin receptor [23,32]. Therefore, gastrin levels can contribute not only to the diagnosis of AIG but also to the pathogenesis of gastric cancer.

A recent retrospective multicenter Japanese registry study conducted by Terao et al. [20] showed that the most common approach to diagnose AIG was endoscopic examination and that typical endoscopic findings can help the diagnosis. Their study demonstrated that corpus pan-atrophy was the most common appearance (90.1%); however, remnant oxyntic mucosa was found in 31.5% of patients, and sticky adherent dense mucus was also observed in approximately 30%. In approximately 40% of patients, atrophy of variable extent was present. Other reports also indicated that proximal-predominant gastric mucosal atrophy was a typical endoscopic finding in patients with AIG [8,18,19]. The prevalence of remnant oxyntic mucosa and sticky adherent dense mucus is not as high, but these are considered highly specific findings. In our study, only in 1 H. pylori-positive patient (case 1), corpus-dominant atrophy was not detected. H. pylori-positive AIG also shows atrophy in the antrum, which may make the diagnosis difficult. If a patient was positive for H. pylori, a diagnosis of AIG may be considered for the first time after eradication treatment.

In our study, a PCA titer of 20-fold or more was defined as positive, because PCA is not an ELISA test but a fluorescent antibody test that is visually determined. Thus, a 10-fold result can be a false-positive. PCA was 10-fold in 7 out of 30 cases, but neither hypergastrinemia nor the typical endoscopic findings of AIG were observed in these cases. As the lesion progresses, PCA is known to decrease due to a decrease in the fundic glands [33]. If PCA has low antibody levels, as in our study, serum gastrin and endoscopic findings should be consulted to determine whether they match those of AIG. In order to improve the diagnostic accuracy of AIG, antibody levels should be taken into consideration.

There were some limitations to this study. First, the small sample size and single-center nature of the study might preclude generalization of the results. In the future, we will consider expanding the study to multiple medical centers in Japan. Second, AIG was defined through endoscopic findings and serological markers, without pathological assessment. A strict diagnosis of AIG requires histological evaluation, but as endoscopy was performed as part of a health check-up, we did not obtain samples of gastric tissues. We would consider the inclusion of a pathological assessment for AIG in future studies.

An early diagnosis of AIG may prevent the late stages of the disease, such as PA, due to vitamin B12 deficiency or peripheral neuropathy and may help identify patients at a high risk of developing either gastric cancer or NET. Overseas, histological findings are the gold standard for the diagnosis of AIG. However, it is difficult to collect tissues in all cases, and the establishment of diagnostic criteria taking into account this difficulty is necessary.

**Conclusion**

Our data showed that AIG is not a rare disease in Japan and that its presence should be considered in the diagnosis of endoscopic SAG of the corpus. PCA titer and serum levels of gastrin and PG I/II ratio are useful diagnostic markers of AIG.

**Ethics**

The study protocol was approved by our institution’s Ethics Committee, and all procedures were performed in accordance with the ethical standards laid down in the Declaration of Helsinki (as revised in Brazil, 2013). All patients provided informed consent prior to their inclusion in the study. This study was registered as UMIN000032192 and was supported from a Takeda Japan Medical Affairs Funded Research Grant 2018.

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**References**

Kamada T, et al., Clinics in Surgery - General Surgery


or more failures of H. pylori eradication. Aliment Pharmacol Ther. incidence of autoimmune gastritis in patients misdiagnosed with two


