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【 CASE REPORT 】

Marked Hypergastrinemia with G-cell Hyperplasia in Two Autoimmune Gastritis Patients

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Abstract:
Gastrin regulates gastric acid secretion, and gastrin secretion itself is regulated by the negative feedback system of gastric acidity. Autoimmune gastritis (AG) is a disease where parietal cells are destroyed, resulting in decreased acid production and an elevated serum gastrin level. We herein report 2 AG cases with marked hypergastrinemia (>5,000 pg/mL). In both cases, 24-hour gastric pH monitoring showed no time when gastric pH was <2, and immunohistochemistry revealed more than 140 gastrin-positive cells per linear millimeter at the antral mucosa. This is the first report to confirm the relationship between marked hypergastrinemia and G-cell hyperplasia with AG.

Key words: gastrin, autoimmune gastritis, G-cell hyperplasia, achlorhydria

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Introduction

Gastrin is an endocrine hormone that regulates gastric acid secretion, and gastrin secretion itself is regulated by the negative feedback system of gastric acidity (1). When we detect hypergastrinemia, we consider the possibility of multiple endocrine neoplasia type 1 Zollinger-Ellison syndrome (ZES) (2). Other causes, such as the use of proton pump inhibitors (PPIs), *Helicobacter pylori*-associated gastritis, and autoimmune gastritis (AG), lead to hypergastrinemia with G-cell hyperplasia. In addition, kidney diseases increase the gastrin level via the retardation of renal excretion (3-5).

In AG, many patients have anti-gastric parietal cell antibodies and/or anti-intrinsic factor antibodies. Anti-gastric parietal cell antibodies target the parietal cell H^+, K^+-ATPase. This leads to the destruction of parietal cells and decreases acid production. As mentioned above, gastrin secretion is regulated by gastric acidity, and this mechanism induces G-cell hyperplasia and hypergastrinemia (6).

One group reported that serum gastrin concentrations were over 1,000 pg/mL in two-thirds of ZES patients in their study (7). However, there have been few reports showing the correlation between serum gastrin levels and the diseases leading to hypergastrinemia, except for ZES.

We herein report two AG cases with marked hypergastrinemia in which G-cell hyperplasia was confirmed with immunohistochemistry.

Case Reports

Case 1

A 65-year-old Japanese woman with hypergastrinemia was admitted to our hospital. She had no history of gastroduodenal ulcer. At 53 years of age, she had been diagnosed with autoimmune thyroiditis. At 60 years of age, she was completely cured of *H. pylori* infection. At 63 years of age, she had been admitted to another hospital because of hypoglycemia. Insulinoma had been ruled out by the 72-hour

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fasting test, and she had been diagnosed with reactive hypoglycemia with the 5-hour 75-g oral glucose tolerance test (OGTT). On admission, her serum gastrin concentration had increased to 5,140 pg/mL, using a PPI. Although she had stopped using the PPI, her serum gastrin concentrations remained over 4,000 pg/mL, so she consulted with our hospital. There was no family history of multiple endocrine neoplasia.

A physical examination was unremarkable. Laboratory results are shown in Table 1. Her serum gastrin concentration was high (4,800 pg/mL; normal range 31-172 pg/mL), and a serum *H. pylori* antibody test was negative (<3 U/mL). Both thyroglobulin antibody and thyroid peroxidase antibody were positive (8.3 U/mL and 144.7 U/mL, respectively). Her intact parathyroid hormone (iPTH) level and corrected serum calcium level were also normal (32.4 pg/mL; normal range 8.7-79.6 pg/mL and 9.4 mg/dL; normal range 8.4-10.0 mg/dL, respectively). Her serum vitamin B_{12} concentration was slightly low (193 pg/mL; normal range 211-911 pg/mL), but her hemoglobin level and mean corpuscular volume (MCV) level were normal (13.4 g/dL; normal range 12.0-15.0 g/dL and 87.5 fL; normal range 84.0-98.0 fL, respectively).

Table 1. Laboratory Data of Case 1.

Index	Date	Unit
White Blood Cells	4,060	/μL
Red Blood Cells	487×10⁴	/μL
Hemoglobin	13.4	g/dL
Mean Corpuscular Volume	87.5	fL
Mean Corpuscular Hemoglobin	27.5	pg
Mean Corpuscular Hemoglobin Concentration	31.5	%
Platelet	23.9×10⁴	/μL
Sodium	143	mEq/L
Potassium	3.9	mEq/L
Chloride	106	mEq/L
Calcium	9.4	mg/dL
Phosphorus	4.2	mg/dL
Total Protein	7.2	mg/dL
Albumin	4.2	mg/dL
C-reactive protein	0.07	mg/dL
Vitamin B12	193	pg/mL
Glycated hemoglobin	5.8	%
Glucose	94	mg/dL
Insulin	6	μU/mL
C-peptide	1.5	ng/mL
TSH	0.82	μU/mL
T4	1.3	ng/dL
Thyroglobulin antibody	8.3	U/mL
Thyroid peroxidase antibody	144.7	U/mL
PTH	32.4	pg/mL
Gastrin	4,800	pg/mL
Glucagon	110	pg/mL
PRL	15.6	ng/mL
ACTH	36	pg/mL
H. Pyroli antibody	<3	U/mL
Anti-gastric parietal cell antibody	Positive	
Ant-intrinsic factor antibody	Positive	

Contrast abdominal computed tomography (CT) detected a small, stained region (maximum diameter, 0.9 mm) in the tail of the pancreas, but contrast endoscopic ultrasound sonography (EUS) and somatostatin receptor scintigraphy (SRS) did not detect a significant signal in that region. Twenty-four-hour gastric pH monitoring showed no time when the gastric pH was <2 (Fig. 1A). Based on these findings, we comprehensively ruled out ZES.

Esophagogastroduodenoscopy (EGD) showed atrophy of the mucosa in the entire stomach body, but no ulcer regions. The degree of atrophy in the antral mucosa was less than in the stomach body. We examined a 6-mm length of the antral mucosa obtained by a biopsy, and gastrin immunohistochemistry revealed 160±24 G-cells/mm in the antral mucosa (Fig. 2A). Synaptophysin staining revealed that the number of endocrine micronests with a maximum diameter of 50-75 μm was 0.83±1.16/mm in the same region, with no endocrine micronests larger than 75 μm in diameter (Fig. 2B).

Because both anti-gastric parietal cell antibody and anti-intrinsic factor antibody were positive, she was diagnosed with AG. Based on these results, her hypergastrinemia was considered to have been caused by G-cell hyperplasia related to the negative feedback system against achlorhydria with AG.

Case 2

A 65-year-old Japanese woman with hypergastrinemia was admitted to our hospital. She had no history of gastroduodenal ulcer. At 45 years of age, she had been diagnosed with autoimmune thyroiditis. At 58 years of age, she had been diagnosed with atrophic gastritis. At 64 years of age, a focal red region had been identified with EGD in the gastric body, and a carcinoid tumor had been confirmed by histology. At that time, she had been using a PPI, and her serum

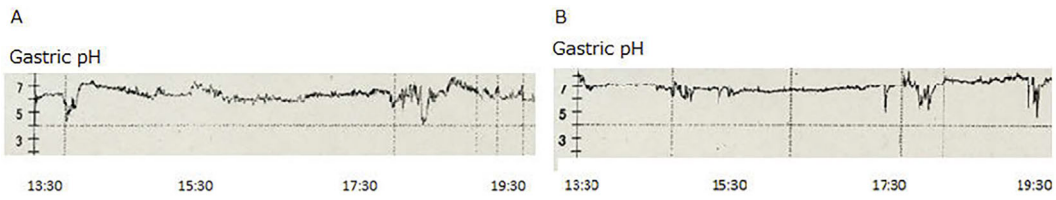

Figure 1. Continuous gastric pH monitoring. There was no time when the gastric pH was<2, even after a meal, in either case (A: case 1, B: case 2).

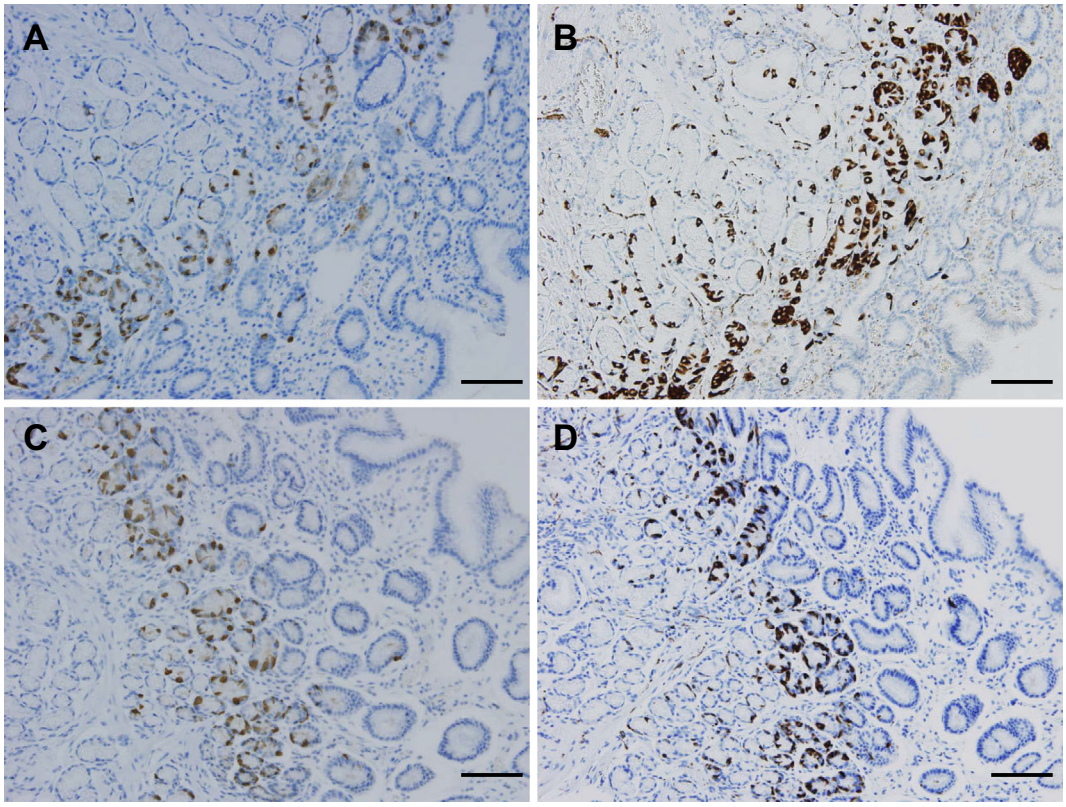

Figure 2. **Gastrin and synaptophysin immunohistochemistry. Case 1 (A: gastrin staining, B: synaptophysin staining), and Case 2 (C: gastrin staining, D: synaptophysin staining). More than 140 gastrin-positive cells per linear mm were detected at the antral mucosa obtained by biopsies, and endocrine micronests were present in both cases. Bar=100 μm (A-D)**

gastrin concentration had been 2,400 pg/mL. She later stopped using the PPI; however, at 65 years of age, her serum gastrin concentration had risen to 5,820 pg/mL, and she consulted our hospital. There was no family history of multiple endocrine neoplasia.

Laboratory results are shown in Table 2. Her serum gastrin concentration was high (1,170 pg/mL), and a serum *H. pylori* antibody test was negative (<3 U/mL). Both thyroglobulin antibody and thyroid peroxidase antibody were positive (695.7 U/mL and 3.7 U/mL, respectively). Her iPTH level and corrected serum calcium level were also normal (40.5 pg/mL and 9.0 mg/dL, respectively). She took vitamin B_{12} because of joint pain, and her serum vitamin B_{12} concentration was high (1,168 pg/mL). Her hemoglobin level and MCV level were normal (12.9 g/dL and 92.8 fL, respectively).

EGD showed Barrett's esophagus and atrophy of the mucosa in the stomach, especially in the gastric body. The carcinoid tumor had already vanished prior to admission. Neither contrast abdominal CT nor EUS detected abnormal findings in the stomach. Twenty-four-hour gastric pH monitoring showed no time when the gastric pH was <2 (Fig. 1B). We examined a 9-mm length of the antral mucosa, and gastrin immunohistochemistry showed 127±31 G cells/mm in the antral mucosa (Fig. 2C). Synaptophysin staining revealed the presence of 0.77±0.66/mm endocrine micronests with a maximum diameter of 50 μm (Fig. 2D).

Because both anti-gastric parietal cell antibody and anti-intrinsic factor antibody were positive, she was also diagnosed with AG, and her hypergastrinemia was considered to have been caused by G-cell hyperplasia related to the negative feedback system against achlorhydria with AG.

Discussion

In both of the above cases, anti-gastric parietal cell antibody and anti-intrinsic factor antibody were serologically positive, and atrophic gastritis was found by EGD. Therefore, both patients were diagnosed with AG. G-cell hyperplasia was confirmed by gastrin immunohistochemistry. As a result, the marked hypergastrinemia of both patients was considered to have been caused by G-cell hyperplasia related to the negative feedback system against achlorhydria with AG. A few previous cases with AG showed marked hypergastrinemia (8, 9), but an immunohistochemical analysis of G-cell hyperplasia was not performed in those cases. This is the first report to confirm the relationship between marked hypergastrinemia and G-cell hyperplasia with AG.

In the present study, G-cell hyperplasia was defined as more than 140 gastrin-positive cells per linear millimeter of appropriately oriented mucosa (10). In case 1, there were more than 140 G cells in all segments, and in case 2, more

Table 2. Laboratory Data of Case 2.

Index	Date	Unit
White Blood Cells	4,950	/μL
Red Blood Cells	416×10^4	/μL
Hemoglobin	12.9	g/dL
Mean Corpuscular Volume	92.8	fL
Mean Corpuscular Hemoglobin	31.0	pg
Mean Corpuscular Hemoglobin Concentration	33.4	%
Platelet	17.7×10^4	/μL
Sodium	142	mEq/L
Potassium	3.7	mEq/L
Chloride	106	mEq/L
Calcium	9.0	mg/dL
Phosphorus	3.6	mg/dL
Total Protein	6.1	mg/dL
Albumin	3.8	mg/dL
C-reactive protein	0.04	mg/dL
Vitamin B12	1,168	pg/mL
Glycated hemoglobin	5.8	%
Free Plasma Glucose	81	mg/dL
Insulin	1.2	μU/mL
C-peptide	4.1	ng/mL
TSH	4.31	μU/mL
T4	1.1	ng/dL
Thyroglobulin antibody	695.7	U/mL
Thyroid peroxidase antibody	3.7	U/mL
PTH	40.5	pg/mL
Gastrin	1,170	pg/mL
Glucagon	25	pg/mL
PRL	15.6	ng/mL
ACTH	25	pg/mL
H. Pyroli antibody	<3	U/mL
Anti-gastric parietal cell antibody	Positive	
Ant-intrinsic factor antibody	Positive	

than 140 G cells were found in several segments. These pathological results indicated that the hypergastrinemia in these patients was caused by G-cell hyperplasia against achlorhydria with AG. In both cases, 24-hour gastric pH monitoring revealed achlorhydria. Recently, it was reported that when hypergastrinemia is found, the gastric pH should be checked first. Then, if the gastric pH is <2, the possibility of gastrinoma should be considered (11). Based on our experience with these two cases, when hypergastrinemia is found, we agree that gastric pH monitoring and EGD are important, in addition to implementing other imaging methods used to search for gastrinoma. Indeed, gastrinoma was suspected in the tail of the pancreas in case 1 based on the findings of contrast abdominal CT but was completely rejected as a possibility only after gastric pH monitoring and EGD had been performed.

While a biopsy is more invasive than other tests, it can be used to examine G cells and ECL cells. Because a previous group reported that ECL cell dysplasia indicates a higher risk of a carcinoid (10), biopsies may be worth performing.

It has been reported that AG and autoimmune thyroiditis often exist together (12), and our cases are consistent with those previous findings. Autoimmune thyroiditis is a common disease with a prevalence of about 10% (13), and 12-40% of autoimmune thyroiditis patients have anti-gastric parietal cell antibody (14). Furthermore, AG and autoimmune thyroiditis are also seen in 3B autoimmune polyendocrine syndrome patients (15). Therefore, on detecting autoimmune diseases such as autoimmune thyroiditis, we should consider the possibility of AG and check the gastrin mucosa and serum gastrin levels.

Finally, case 1 also had reactive hypoglycemia. The OGTT showed that her plasma glucose level had increased to 206 mg/dL at 60 minutes after taking 75 g of glucose, while her insulin levels had dramatically increased to 220.2 μU/mL. Her reactive hypoglycemia seemed to indicate a prediabetic state. Although there has been no report about the association between hypergastrinemia and reactive hypoglycemia in humans, it has been reported that gastrin is one factor stimulating β-cell neogenesis in islets (16). The hypergastrinemia in this case might therefore have been related to the patient's excessive insulin secretion.

In conclusion, we herein report the first two cases of AG with marked hypergastrinemia in which G-cell hyperplasia was confirmed with immunohistochemistry. Achlorhydria associated with AG should be recognized as a cause of marked hypergastrinemia, especially when patients have other autoimmune diseases, such as autoimmune thyroiditis.

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

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