〈Case Report〉

Four cases of gastric cancer in patients with autoimmune gastritis

Kazuhiro YOSHIDA [1)], Tomoki YAMATSUJI [1)], Masaki MATSUBARA [1)], Takuya FUKAZAWA [1)], Jiro HAYASHI [1)], Munenori TAKAOKA [1)], Yoshio NAOMOTO [2)], Miwa KAWANAKA [3)], Tomohiro TANIKAWA [3)], Jun NAKAMURA [3)], Mitsuhiko SUEHIRO [3)], Yasumasa MONOBE [4)], Ken HARUMA [3)], Hirofumi KAWAMOTO [3)]

1) Kawasaki Medical School, Department of General Surgery, Kawasaki Medical School General Medical Center,
2) Kawasaki Medical School General Medical Center,
3) Kawasaki Medical School, Department of General Internal Medicine, Kawasaki Medical School General Medical Center,
4) Kawasaki Medical School, Department of Pathology, Kawasaki Medical School General Medical Center

ABSTRACT Here, we report on four cases of gastric cancer in patients with autoimmune gastritis (AIG). AIG is characterized by the corpus-predominant atrophic gastritis with preserved antrum caused by autoimmune mechanisms. Although AIG is a high risk factor for gastric cancer and neuroendocrine tumors (NET), there are few reports describing the characteristics of gastric cancer in patients with AIG. In this case report, all four cases were diagnosed as having AIG by endoscopic findings and the presence of extra-gastric autoimmune diseases before the treatment for gastric cancer. doi：10.11482/KMJ-E201945075 *(Accepted on June 14, 2019)*

Key words：Gastric cancer, Autoimmune gastritis, Hypergastrinemia

INTRODUCTION

Autoimmune gastritis (AIG), also known as type A gastritis, is characterized by atrophic changes in the fundic mucosa. It is caused by autoimmune mechanisms, such as anti-parietal cell antibodies (PCA), which lead to hypergastrinemia and cause hyperplasia of enterochromaffin-like cells, resulting in complications such as hyperplastic polyps, neuroendocrine tumors (NETs), and gastric cancer[1－6)]. AIG is commonly diagnosed via medical examination of patients with pernicious anemia (PA) or type-1 NETs, and it is associated with autoimmune thyroid disease[7, 8)] or type-I diabetes mellitus (DM)[9, 10)]. In Japan, AIG is thought to be a rare disease[11)] and there is no data about the prevalence of AIG because it is asymptomatic in its initial stage. In its late stage, AIG might cause PA characterized by megaloblastic anemia and be diagnosed in clinical practice. In previous clinical statistical data gathered by Sugihara T and Yawata Y, the estimated prevalence of PA caused by AIG was 0.34 to 0.5 per 100,000 people in Japanese[12)]. Recently we diagnosed four cases of gastric cancer in patients with AIG

Corresponding author
Yoshio Naomoto
Kawasaki Medical School General Medical Center, 2-6-1, Nakasange Kita-ku, Okayama, 700-8505, Japan
Phone : 81 86 225 2111
Fax : 81 86 232 8343
E-mail: ynaomoto@med.kawasaki-m.ac.jp

between April 2015 and December 2018. Because AIG is thought to be a rare disease in Japan, we are reporting on the clinical characteristics that we observed with an emphasis on endoscopic findings and also on the history of using the presence of autoimmune diseases to diagnose AIG. The presence of ECM（composed of hyperplastic ECL cells）is one of characteristic histologic findings of AIG, and immunohistochemically can be detected by chromogranin A antibody (neuroendocrine marker).

In this study, we defined AIG as the presence of corpus-predominant atrophic gastritis with hypergastrinemia and PCA and/or the presence of endocrine cell micronest (ECM) in the corpus mucosa.

CASE REPORT

The characteristics of four cases of gastric cancer developed from AIG are shown in the Table 1. Three were females and all were over 75 years old. Three cases located in the antrum were diagnosed at an early stage. Histology of the gastric cancer indicated well-differenciated adenocarcinoma in two cases, signet-ring cell carcinoma in one, and mucinous adenocarcinoma in one. All four cases had multiple hyperplastic polyps in the corpus. ECMs in the corpus were documented in three cases (cases 1, 2, and 4, Fig. 1-6). Cases 3 and 4 were tested for PCA and the results were positive. Intrinsic factor antibody was not tested for in any of the cases and none of the cases were shown to have PA.

Case 1.

An 83-year-old Japanese woman was referred to our Department of Surgery for gastric cancer surgery. This patient had a history of hypothyroidism and atrial fibrillation. An esophagogastroduodenoscopy revealed a type 0-IIc+IIa gastric cancer in the lesser body and severe atrophic gastritis in the fundus, whereas no atrophic change was seen in the antrum (Fig. 1,2 and 3). The fasting gastrin level was 1,954 pg/ml (normal range; 5 - 150 pg/ml) and ECMs were documented in the corpus after the surgical operation.

Case 2.

An esophagogastroduodenoscopy was performed on an 83-year-old Japanese woman due to increased CA19-9 levels and revealed type 1 gastric cancer in the lesser antrum and corpus-predominant atrophic gastritis (Fig. 4,5 and 6). The patient had a history of type 1 diabetes mellitus (DM), hypothyroidism and renal failure. The fasting gastrin level was 6,333 pg/ml and ECMs were documented in the corpus after the surgical operation.

Cases 3 and 4.

These two cases both had a history of type C hepatitis and hepatocellular carcinoma (HCC) and were diagnosed with early gastric cancer after an examination of the esophageal varix. Both cases were completely resected by endoscopic therapy. The fasting gastrin level was 7,445 pg/ml in case 3 and 2,848 pg/ml in case 4. PCA was positive in both cases.

DISCUSSION

In this case report, AIG was diagnosed based

Table 1. Characteristics of four cases of gastric cancer developed from AIG

No.	Age	Sex	Type	Location of tumor	Depth	Histology	Gastrin (pg/ml)	ECM	Co-existing lesions
1	83	F	0-IIc+IIa	Lesser corpus	SM2	sig > muc > por	1954	+	HP
2	84	F	1	Lesser antrum	MP	muc > tub1	6334	+	HP
3	80	M	0-I	Anterior antrum	M	tub1	7445	NT	HP
4	75	F	0-IIa	Posterior antrum	M	tub1	2848	+	HP

AIG; Autoimmune gastritis, ECM; Endocrine cell micronest, NT; Not tested, HP; Hyperplastic polyps

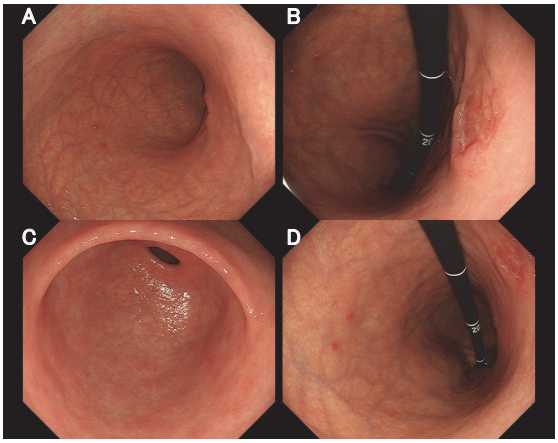

Fig. 1. Endoscopic feature of case 1.
A: Corpus of the stomach; B: type0-IIc tumor located in the lessor antrum; C: Antrum, D: Fornix and corpus The gastroscopy shows severe atrophic gastritis demonstrating disappearing of the visible vascular patterns and the giant rugae in the corpus and body of the stomach (A,D), whereas no atrophic change is seen in the antrum (C).

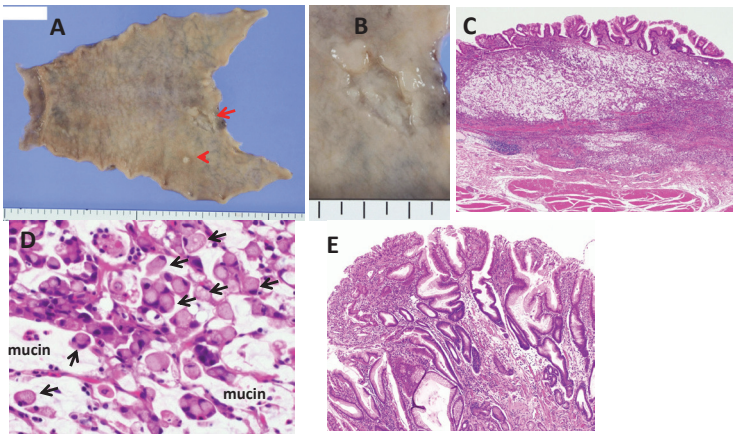

Fig. 2. Gross and histological findings of case 1.
A. A gross figure of stomach showing Type 0-IIc+IIa gastric cancer (arrow) is located in the lesser body, and severe atrophic gastritis in the fundus is found, whereas no atrophic change is seen in the antrum. A hyperplastic polyp (arrowhead) is found in the posterior wall. B. Close-up picture of Type 0-IIc+IIa gastric cancer (27x14mm in size) C. (Hematoxylin-eosin、10x4) The gastric cancer with mucin production is seen in the gastric mucosa spreading to submucosa. D. (Hematoxylin-eosin、10x60) Many signet ring cells (arrows) are seen in the mucinous matrix. E. (Hematoxylin-eosin、10x20) A hyperplastic polyp is composed of hyperplastic foveolar epithelium.

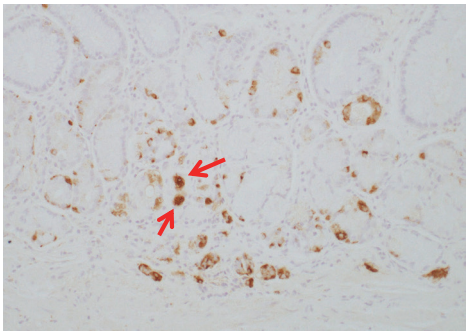

Fig. 3. Chromogranin A staining of atrophic gastric mucosa.
Arrows indicate endocrine cellular micronests (ECMs) are positive for chromogranin A.

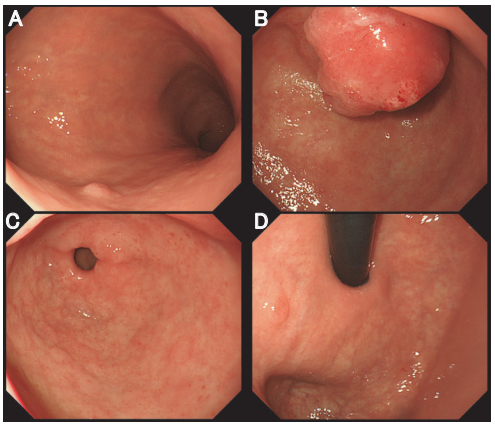

Fig. 4. Endoscopic features of case 2.
A: Corpus of the stomach; B: type 1 tumor located in the lessor antrum; C: Antrum, D: Fornix/cardia Almost same findings of severe atrophic gastritis as in Figure 1 are confirmed in A-D.

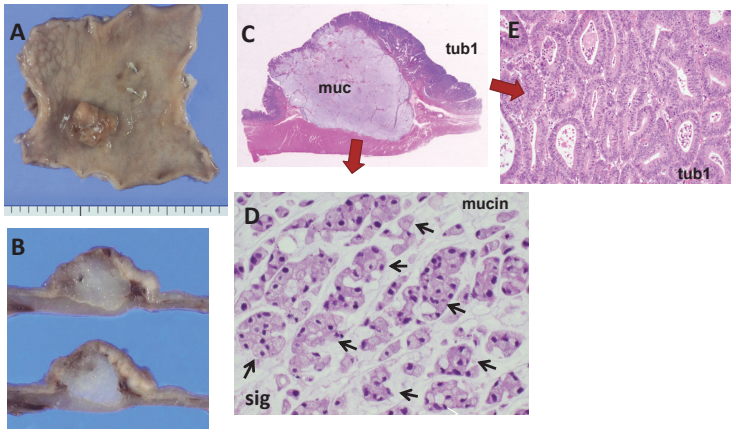

Fig. 5. Gross and histological findings of case 2.
A: Gross figure of stomach shows Type 1 gastric cancer located in the lesser antrum and corpus with severe atrophic gastritis. B. The cut surface of the tumor shows a tumor containing abundant mucinous element. C. A lupe figure shows the tumor with two components of mucinous carcinoma (muc) containing signet ring cell carcinoma (sig) and tubularadenocarcinoma (tub1). D. (Hematoxylin-eosin、10x40) Mucinous carcinoma is composed of signet ring cell carcinoma (sig, arrows) and abundant mucinous matrix (muc). E. (Hematoxylin-eosin, 10x20) Tubular adenocarcinoma (tub1) shows well differentiated tubular structures. Gross findings: Type 1 gastric cancer is located in the lesser antrum, and corpus with severe atrophic gastritis was found. Microscopic findings: The cancer was composed with two components (arrows), mucinous adenocarcinoma (muc) with signet ring cell carcinoma (sig), and well differentiated tubular adenocarcinoma (tub1).

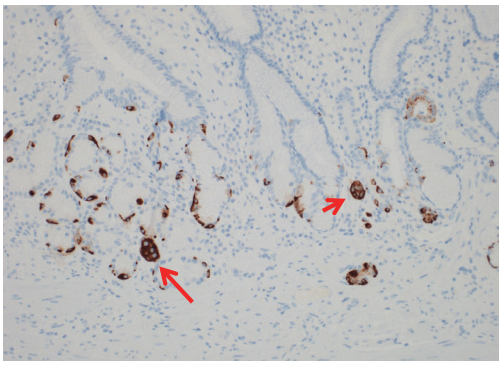

Fig. 6. Chromogranin A staining of atrophic gastric mucosa.
Immunohistochemical staining (Chromogranin A, 10x20), Arrows indicate endocrine cell micronests (ECMs) with chromogranin A.

on endoscopic findings (corpus-predominant atrophic gastritis, the presence of multiple gastric hyperplastic polyps), and the coexistence of extra-gastric autoimmune diseases (hypothyroidism and type 1 diabetes mellitus) at the time of the gastric cancer diagnosis. AIG is characterized by the presence of severe corpus-predominant atrophic gastritis with hypergastrinemia and PCA and/or the presence of ECM in the corpus mucosa, while also being known as a high risk for gastric cancer and NET[1-6].

In our previous study, patients with a fasting gastrin level of ≥ 245.1 pg/mL were considered as having hypergastrinemia[13]. In this report, extremely high gastrin levels were found in all four cases (1,954 pg/ml, 6,334 pg/ml, 7,445 pg/ml, and 2,848 pg/ml). Because gastrin is known to be a growth factor for gastric cancer and NET[14-17], extreme hypergastrinemia may have played a role in the carcinogenesis in these four cases.

In this case report, three of the four cases were polypoid type gastric cancer and the remaining one had polypoid components in the gastric lesion. Our previous study of 957 patients with early gastric cancer indicated that serum gastrin levels were significantly higher in patients with elevated tumors than in patients with depressed tumors and have the possibility to enact morphological change in the gastric cancer through the gastrin receptor[18]. Therefore, the determination of gastrin levels contributes not only to the diagnosis of AIG but also to the pathogenesis of gastric cancer.

AIG is associated with extra-gastric autoimmune diseases such as autoimmune thyroid disease[7, 8] and type 1 DM[9, 10]. Two of our cases had hypothyroidism mainly caused by autoimmune thyroiditis, and one also had type 1 diabetes mellitus. The coexistence of at least two autoimmune-mediated endocrinopathies is known as polyglandular autoimmune syndrome (PSA), which was further classified into four types by Neufeld M and Blizzard R[19-21]. Case 1 had hypothyroidism and would be classified as APS type 3 (autoimmune thyroid disease + autoimmune gastritis). Case 2 could be called APS type 4 (autoimmune thyroid disease + type 1 DM + autoimmune gastritis).

Although APS is thought to be a rare disease, it is important to suspect APS in patients with one autoimmune disease. Even though two patients (cases 3 and 4) had HCC with type C hepatitis, no association between AIG and HCC has been previously reported. Because the presence of extra-hepatic malignancies is one important risk factor associated with the prognosis of HCC, a check for common malignancies, including gastric cancer, is important. Our two cases (case 3 and 4) were diagnosed at an early stage without any gastrointestinal symptoms related to gastric cancer due to a follow-up endoscopy for the esophageal varix and could be completely treated by endoscopic therapy.

All four cases had multiple hyperplastic polyps in the corpus. It is important to determine the gastrin level for the screening of AIG in patients with gastric hyperplastic polyps because previous studies, including our own, have indicated that AIG is closely related to gastric polyps[11, 13, 22, 23]. Park JY et al. reported that there were 240 endoscopically or grossly identifiable lesions in the stomach in 143 of 461 (31%) patients with AIG and the lesions consisted of 138 hyperplastic polyps[22]. Zhang H. et al. also indicated in a study of 320 patients with AIG that 63 patients (19.7%) with AIG had gastric hyperplastic polyps[23]. In addition, other previous studies have indicated that AIG is common in patients with gastric polyps and gastric polyps are common in patients with pernicious anemia, the late stage of AIG[24].

An early diagnosis of AIG may prevent the latent stage of this disease, pernicious anemia, due to vitamin B12 deficiency or peripheral neuropathy and may help identify patients at a high risk

for developing either gastric cancer or NET. As reported here, careful endoscopic observation of the gastric mucosa to identify corpus-predominant atrophic gastritis, gastric hyperplastic polyps and extra-gastric autoimmune diseases might help to diagnose AIG. Hemoglobin and MCV(Mean Corpuscular Volume) of our cases were 10.9 g/dl and 90.7fl in case 1, 10.2 g/dl and 97.2 fl in case 2, 14.2 g/dl and 95.9 fl in case 3, 8.8g/dl and 88.5 fl in case 4. Therefore, all four cases did not show the remarkable findings of pernicious anemia. The serum vitamin B12 level were not measured in all four cases.

Mahmud N et al. showed that AIG is associated with a high prevalence and incidence of gastric cancer, and endoscopic surveillance should be considered in all patients with AMAG, especially in patients with advanced age (≥ 70 years). While endoscopic surveillance at 3 years appears reasonable, prospective cohort studies and cost effectiveness analyses are clearly needed to further define the estimated risk of cancer in patients with AIG and to refine recommended surveillance intervals[25]. Park JY et al. indicated that the important clinical findings include anemia (microcytic or macrocytic) or endocrine dysfunction (diabetes mellitus, autoimmune thyroiditis)[26]. Although pernicious anemia and AIG have been recognized for more than 100 years, it is still in the infancy of recognizing the early presentation of AIG and standardizing our management of these patients26). These suggestions are objectively appropriate.

REFERENCES

1） Strickland RG, Mackar IR: A reappraisal of the nature and significance of chronic atrophic gastritis. Am J Dig Dis 18: 426-440, 1973

2） Stockbrugger RW, Menon GG, Beilby JO, Mason RR, Cotton PB. Gastroscopic screening in 80 patients with pernicious anemia. Gut 24: 1141-1147, 1983

3） Lam-Tse WK, Batstra MR, Koeleman BP, Roep BO, Bruining MG, Aanstoot HJ, Drexhage HA. The association between autoimmune thyroiditis, autoimmune gastritis and type 1 diabetes. Pediatr Endocrinol Rev 1: 22-37, 2003

4） Minalyan A, Benhammou JN, Artashesyan A, Lewis MS, Pisegna JR. Autoimmune atrophic gastritis: current perspectives. Clin Exp Gastroenterol 10: 19-27, 2017

5） Irvine WJ. The association of atrophic gastritis with autoimmune thyroid disease. Clin Endocrinol Metab 4: 351-377, 1975

6） Whittingham S, Youngchaiyud U, Mackay IR, Buckley JD, Morris PJ. Thyrogastric autoimmune disease. Studies on the cell-mediated immune system and histocompatibility antigens. Clin Exp Immunol 19: 289-299, 1975

7） Utiyama SRR, De Bem RS, Skare TL, De Carvalho GA, Teixeira LM, Bertolazo M, Ioshii SO, Nisihara R. Anti-parietal cell antibodies in patients with autoimmune thyroid diseases. J Endocrinol Invest 41: 523-529, 2018

8） Castoro C, Le Moli R, Arpi ML, Tavarelli M, Sapuppo G, Frittitta L, Squatrito S, Pellegriti G. Association of autoimmune thyroid diseases, chronic atrophic gastritis and gastric carcinoid: experience from a single institution. J Endocrinol Invest 39: 779-784, 2016

9） Kahaly GJ, Hansen MP. Type 1 diabetes associated autoimmunity. Autoimmun Rev 15: 644-648, 2016

10） Pan XF, Gu JQ, Shan ZY. Type 1 Diabetic Populations Have an Increased Prevalence of Parietal Cell Antibody: A Systematic Review and Meta-Analysis. Medicine (Baltimore) 94: e1440, 2015

11） Haruma K, Komoto K, Kawaguchi H, Okamoto S, Yoshihara M, Sumii K, Kajiyama G. Pernicious anemia and Helicobacter pylori infection in Japan: evaluation in a country with a high prevalence of infection. Am J Gastroenterol 90: 1107-1110, 1995

12） Sugihara T, Yawata Y. Japanese clinical statistical data of patients with pernicious anemia. Nihon Rinsho 50: 771-786, 1992 (Article in Japanese)

13） Haruma K, Yoshihara M, Sumii K, Tari A, Watanabe C, Kodoi A, Kajiyama G. Gastric acid secretion, serum pepsinogen I, and serum gastrin in Japanese with gastric hyperplastic polyps or polypoid-type early gastric carcinoma. Scand J Gastroenterol 28: 633-637, 1993

14） Morris DL, Watson SA, Durrant LG, Harrison JD. Hormonal control of gastric and colorectal cancer in

man. Gut 30: 425-429, 1989

15) S Shao Y, Sun K, Xu W, Li XL, Shen H, Sun WH. Helicobacter pylori infection, gastrin and cyclooxygenase-2 in gastric carcinogenesis. World J Gastroenterol 20: 12860-12873, 2014

16) Smith JP, Nadella S, Osborne N. Gastrin and Gastric Cancer. Cell Mol Gastroenterol Hepatol 4: 75-83, 2017

17) Chen WC, Warner RRP, Harpaz N, Zhu H, Roayaie S, Kim MK. Gastric Neuroendocrine Tumor and Duodenal Gastrinoma With Chronic Autoimmune Atrophic Gastritis. Pancreas 48: 131-134, 2019

18) Ito M, Tanaka S, Maeda M, Takamura A, Tatsugami M, Wada Y, Matsumoto Y, Yoshihara M, Haruma K, Chayama K. Role of the gastrin-gastrin receptor system in the expansive growth of human gastric neoplasms. Digestion 78: 163-170, 2008

19) Neufeld M, Maclaren N, Blizzard R. Autoimmune polyglandular syndromes. Pediatr Ann 9: 1541-62, 1980

20) Betterle C, Zanchetta R. Update on autoimmune polyendocrine syndromes (APS). Acta Biomed 74: 9-33, 2003

21) Husebye ES, Anderson MS, Kämpe O. Autoimmune Polyendocrine Syndromes. N Engl J Med 378: 1132-1141, 2018

22) Park JY, Cornish TC, Lam-Himlin D, Shi C, Montgomery E. Gastric lesions in patients with autoimmune metaplastic atrophic gastritis (AMAG) in a tertiary care setting. Am J Surg Pathol 34: 1591-1598, 2010

23) Zhang H, Jin Z, Cui R, , Ding S, Huang Y, Zhou L. Autoimmune metaplastic atrophic gastritis in chinese: a study of 320 patients at a large tertiary medical center. Scand J Gastroenterol 52: 150-156, 2017

24) Laxén F. Gastric carcinoma and pernicious anaemia in long-term endoscopic follow-up of subjects with gastric polyps. Scand J Gastroenterol 19: 535-540, 1984

25) Mahmud N, Stashek K, Katona BW, Tondon R, Shroff SG, Roses R, Furth EE, Metz DC. The incidence of neoplasia in patients with autoimmune metaplastic atrophic gastritis: a renewed call for surveillance. Ann Gastroenterol 32: 67-72, 2019

26) Park JY, Lam-Himlin D, Vemulapalli R. Review of autoimmune metaplastic atrophic gastritis. Gastrointest Endosc 77: 284-292, 2013