

## Multiple Gastric Carcinoids Associated with Hypergastrinemia. A Review of Five Cases with Clinicopathological Analysis and Surgical Strategies

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**Abstract.** *Previously, total gastrectomy was regarded as the treatment for multiple gastric carcinoids because of the unknown biological characteristics of this disease. Recent studies, however, have revealed that type 1 gastric carcinoids have a low potential for malignancy. In this study, five patients with hypergastrinemia and multiple gastric carcinoids, who underwent gastrectomy with regional node dissection, were analyzed. On serum chemistry examinations, the serum gastrin level was found to be high (515.5-over 3000 pg/ml) in all patients pre-operatively, but returned to a normal range (40-50 pg/ml) in all three cases examined post-operatively. Histopathological examination of our five cases revealed multiple gastric tumors, i.e. three to five tumors in Cases 1-4 and numerous tumors in Case 5. The multiple tumors were histologically carcinoid tumors up to 15 mm in size, limited to the submucosa, and no lymph node metastasis was identified in any of the cases. The patients were followed-up at outpatient clinics with no additional adjuvant therapy, and there was no evidence of recurrence during follow-up. Recently, minor invasive surgery such as endoscopic mucosal resection or laparoscopic antrectomy has been performed to treat type 1 gastric carcinoids. Our data provide important insights into understanding the biological behavior of multiple gastric carcinoids.*

Endocrine cells of the gastrointestinal tract are widely distributed along the entire length of the tract and are interspersed between the epithelial cells. Carcinoid tumors are thought to arise from the endocrine cells, classically

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called enterochromaffin cells. Carcinoid tumors of the stomach are rare, constituting approximately 4% of all gastrointestinal carcinoids (1).

Previous studies have reported a histopathological relationship between endocrine cells and chronic gastritis. The common type of atrophic gastritis, type B gastritis, involves the antral mucosa, while the specific type of gastritis is exclusively confined to the fundic mucosa. The latter is called type A gastritis (2), reversed atrophic type gastritis, or nonantral gastric atrophy (3), and is a characteristic of pernicious anemia. The development of both endocrine cell micronests (ECM) and carcinoids is closely related to atrophic change of the fundic mucosa and the trophic action of the subsequently raised serum levels of gastrin in type A gastritis. In addition, neoplastic ECM (microcarcinoid) of the stomach was defined by a comparative study on both cases of ECM and multiple carcinoids and cases of ECM alone (4).

Hypergastrinemia is known to play a role in the pathogenesis of type 1 gastric carcinoids, as classified by Rindi *et al.* (5-7). Type 1 carcinoids have been associated with type A gastritis and are frequently found as multiple and simultaneous lesions, which display slow growth and benign-like behavior.

Previous reports have demonstrated the regression of multiple carcinoids and/or ECM after the normalization of serum gastrin levels, *i.e.* after gastric antrectomy.

In this paper, five rare cases of surgically resected multiple carcinoids of the stomach are described, and their clinicopathological features are characterized using histological and immunohistochemical procedures.

### Materials and Methods

*Patients and tumors.* The study group comprised five patients diagnosed with multiple gastric carcinoids at the Tokai University Hospital, Japan. One patient was male and four were female. The

Table I. Clinical data for 5 patients with multiple gastric carcinoids.

Case	1	2	3	4	5
Age/Sex	56/F	49/F	42/F	62/M	54/F
Gastric juice examination					
BAO(mEq/h)	0	0	0	0	ND
MAO(mEq/h)	0	0	0	0.008	ND
Pre-operative gastrin (pg/ml)	2600	515.5	>1600	>1600	>3000
Post-operative gastrin(pg/ml)	ND	50.5	46.9	ND	40
Antibody test					
Intrinsic factor antibody	ND	(-)	(-)	ND	(-)
Parietal cell antibody	ND	(-)	(-)	ND	160
Pernicious anemia	(-)	(-)	(-)	(-)	(+)
Number of tumors	4	4	2	3	multiple
Background mucosa	F	F-C	F	F	F-C
Intestinal metaplasia	(+)	(+)	(-)	(+)	(+)
Size of maximum tumor (mm)	3	5	4	15	5
Operation	Total gastrectomy	Total gastrectomy	Total gastrectomy	Total gastrectomy	Total gastrectomy
Prognosis	alive 5y8m af op	alive 11y3m af op	alive 12y10m af op	alive 9y2m af op	alive 0y8m af op

y: years, m: months, af op: after operation, ND: not done, F: fundic mucosa, C: cardiac mucosa

age range was 42-62 (mean  $52.6 \pm 7.5$ ) years. The five patients were endoscopically diagnosed with multiple gastric carcinoids and underwent a total gastrectomy with lymph node dissection. They were followed-up at outpatient clinics with no additional adjuvant therapy.

**Immunohistochemical analysis.** Each tissue specimen was fixed with 10% buffered formalin. Immunohistochemistry was performed with 5- $\mu$ m-thick sections. Deparaffinized and dehydrated sections were immersed in 0.3% hydrogen peroxide (H<sub>2</sub>O<sub>2</sub>) in methanol for 30 min to stop endogenous peroxidase activity. Non-specific binding was prevented with diluted normal sheep serum (Cosmo Bio Co. Ltd., Tokyo, Japan). Next, the sections were overlaid with primary monoclonal antibodies diluted with 1% bovine serum albumin containing phosphate-buffered saline (PBS) and left overnight at 4°C in a moist chamber. As primary antibodies, the following mouse monoclonal antibodies were used: chromogranin A (#2166, 1:200 dilution, Immunotech S.A., Marseille Cedex, France) and synaptophysin (#A 0010, 1:100 dilution, DAKO A/S, Copenhagen, Denmark). Immunoreactivity was detected by an indirect method with our modifications (8). After being washed with PBS, the secondary biotinylated antibody, anti-mouse Ig(Fab)<sub>2</sub> antibody at 1:100 (Amersham International Plc., Buckinghamshire, UK), was applied for 60 min at room temperature. The sections were then treated with the Streptavidin-conjugated horseradish peroxidase for

Table II. Histological data for 5 patients with multiple gastric carcinoids.

Case	1	2	3	4	5
Histological diagnosis	mct	mct	mct	mct	mct
Depth of invasion	sm	sm	sm	sm	sm
Lymphatic permeation	(-)	(-)	(-)	(-)	(-)
Venous permeation	(-)	(+)	(+)	(+)	(-)
Lymph node metastasis	(-)	(-)	(-)	(-)	(-)
Type A gastritis (Atrophic gastritis)	(+)	(+)	(+)	(+)	(+)
Endocrine cell micronests	(+)	(+)	(+)	(+)	(+)
Immunohistochemical and special staining					
Chromogranin A	(+)	(+)	(+)	(+)	(+)
Synaptophysin	(+)	(+)	(+)	(+)	(+)
Grimeilus argyrophil	(+)	(+)	(+)	(+)	(+)

mct: multiple carcinoid tumors, sm: submucosa.

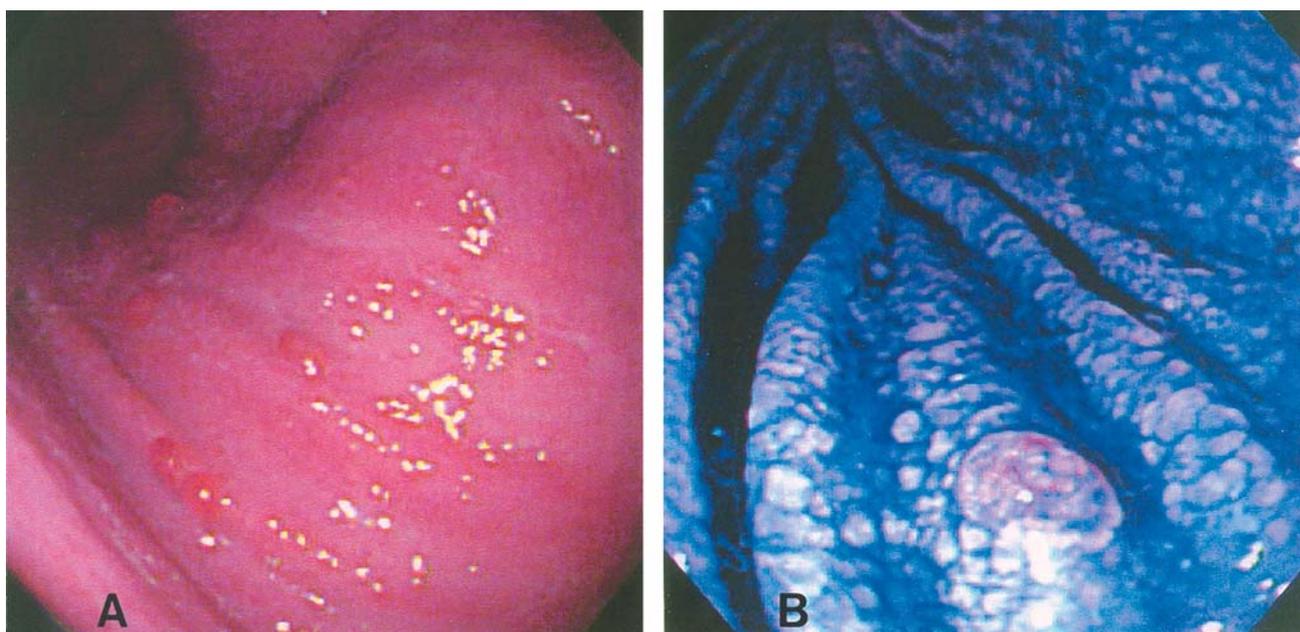


Figure 1. Endoscopic and gross appearance of multiple carcinoid tumors. Multiple small tumors measured less than 5 mm in diameter, and were reddish elevated lesions located in the corpus to fundus without a central depression on their surface (Case 5), (A; conventional endoscopic view), (B; chromoendoscopic view with indigocarmine staining).

30 min at room temperature. The reaction products were visualized using diaminobenzidine tetrahydrochloride (DAB) for 4 min in Tris buffer. Counter-staining was performed using hematoxylin.

## Results

The five patients were asymptomatic on diagnosis, but were all diagnosed with multiple gastric carcinoids by screening endoscopic examinations (Table I). The acid output test revealed achlorhydria, *i.e.* average basal acid output (BAO) of 0.00 mEq/h and average maximal acid output (MAO) of 0.002 mEq/h (Cases 1-4); and a pH of 8.0 in the gastric juice (Case 5). The pre-operative serum gastrin levels were high, at over 515.5 pg/ml (normal range, 25-100 pg/ml) in all patients, and decreased to within the normal range (40-50 pg/ml) post-operatively. The intrinsic factor antibody was negative in three cases examined, while the parietal cell antibody was negative in two cases and positive (>160) in one. The serum vitamin B<sub>12</sub> level was 150 pg/ml (normal range, 233-914 pg/ml) in one case (Case 5). Barium contrast studies detected small elevated tumors in the gastric corpus or fundus in all cases.

Gastroendoscopic evaluations demonstrated multiple polypoid lesions and atrophic changes of the gastric fundic mucosa. The multiple polypoid lesions were up to 15 mm in diameter and exhibited a reddish color (Figure 1). After the endoscopic examinations, all patients underwent a total gastrectomy and lymph node dissection. Histopathological

examinations of the resected specimens demonstrated multiple tumors, *i.e.* three to five tumors in Cases 1-4 and numerous tumors in Case 5 (Table II). The multiple tumors were histologically carcinoid tumors up to 15 mm in size, limited to the submucosa (Figure 2). The background of the carcinoid tumors was mainly fundic mucosa. Intestinal metaplasia was found in four of the five cases (Figure 3). Endocrine cell micronests were identified in all cases. Based on the above histological findings, the patients were all diagnosed with multiple gastric carcinoids accompanied by type A gastritis. The subjects were followed-up at outpatient clinics with no additional adjuvant therapy, and there was no evidence of recurrence during follow-up (range 4-144 months; median 108.4 months).

## Discussion

Gastric carcinoid tumors were previously believed to be rare lesions, representing less than 2% of all carcinoid tumors and less than 1% of all stomach neoplasms (9-11). More recent studies have demonstrated that they may constitute as much as 10-30% of carcinoid tumors in Europe, and 27.3-41% in Japan (12-14). This increase does not reflect a true increase of incidence, but rather is probably due to the increased use of endoscopy and the application of immunohistochemical methods. Clinically, gastric carcinoid tumors may be

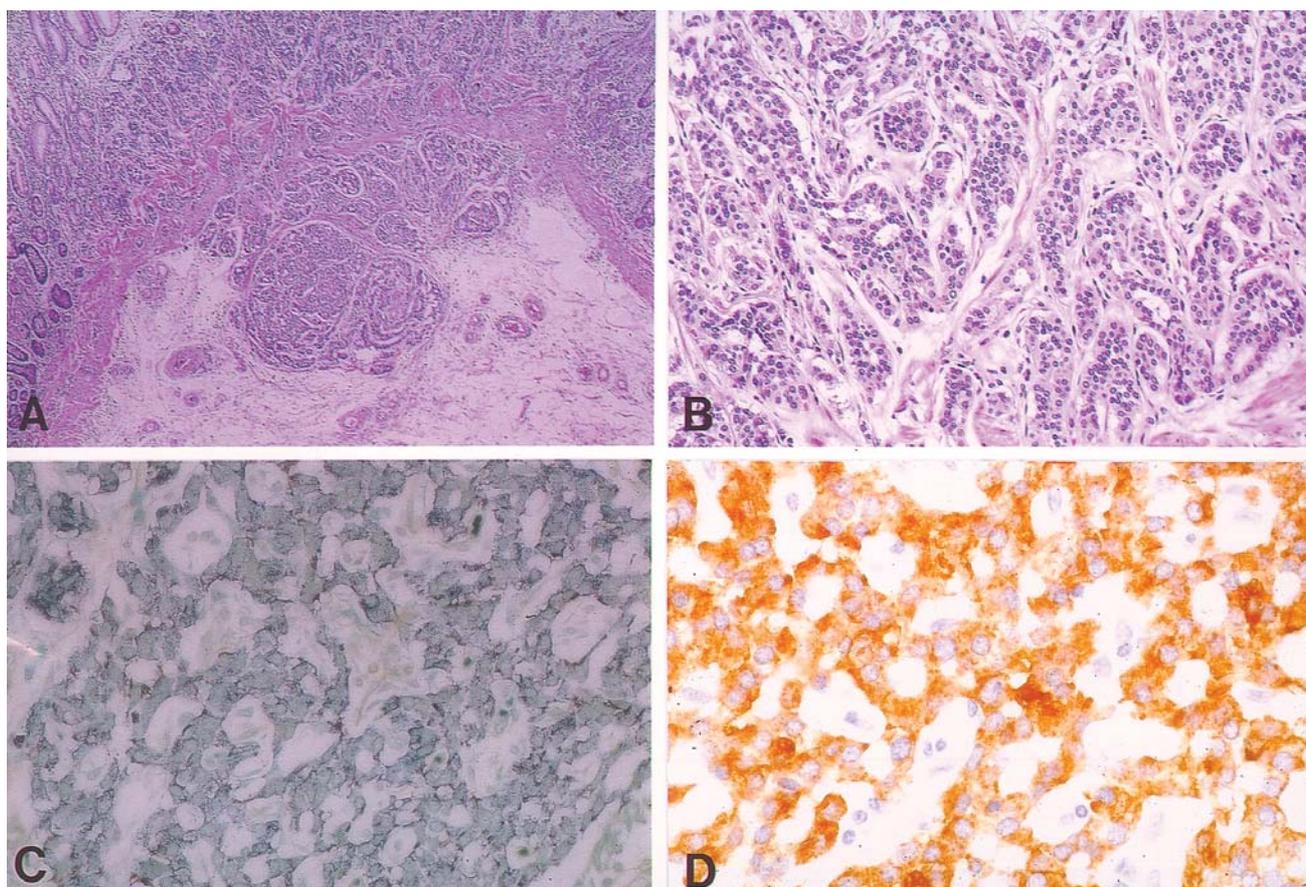


Figure 2. Microscopic and immunohistochemical findings of a carcinoid tumor. Carcinoid tumor cell nests occurred mainly in the mucosal layer and invaded minimally the submucosal layer. Small and solid cell nests, i.e. neuroendocrine cell micronests (ECM), were also present in the surrounding propria mucosa (A; hematoxylin-eosin, x100), (B; hematoxylin-eosin, x400). The carcinoid tumor cells and ECM were argyrophil (C; Grimelius procedure, x400) and immunohistochemically positive for chromogranin A (D; indirect method, x400) and synaptophysin. Most ECM measured less than 0.1 mm, and were located in the deep lamina propria. Some ECM extended into the muscularis mucosae.

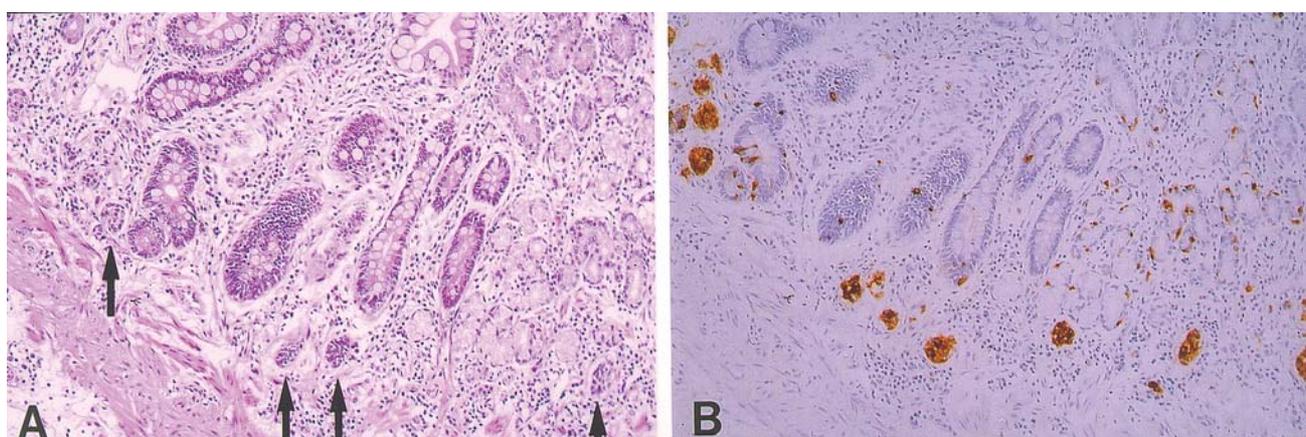


Figure 3. Microscopic and immunohistochemical findings of the background gastric mucosa. Under the atrophic fundic glands, a decrease of parietal and chief cells and a proliferation of mucous cells occurred. There were numerous ECM in the deep lamina propria (A; hematoxylin-eosin, x100), (B; chromogranin A, indirect method, x100).

incidentally identified or may present with symptoms similar to ulcers, gastric polyps, or carcinoma (9). Soga reported that gastric carcinoids were frequently symptomatic with nonspecific manifestations, such as abdominal pain, hematemesis and/or melena (13). The five patients described in this paper were asymptomatic on diagnosis, and were all diagnosed as having multiple gastric carcinoids by endoscopic examination. Hypergastrinemia and achlorhydria/hypochlorhydria were reported in 50.0% and 28.2% of multiple gastric carcinoids, respectively (13, 15-17). All of our five patients exhibited achlorhydria and hypergastrinemia on preoperative examinations, and the serum gastrin level returned to the normal range in all three cases examined post-operatively.

Rindi *et al.* have classified carcinoids associated with enterochromaffin-like cells, which account for the majority of gastric carcinoids, into three types: those linked with chronic atrophic gastritis type A (type 1); those associated with multiple endocrine type 1 adenomas and Zollinger-Ellison syndrome (type 2); and sporadic gastric carcinoid tumors unaccompanied by hypergastrinemia (type 3) (5). Type 1 tumors, associated with chronic atrophic gastritis type A, are the most common type of gastric carcinoids and are characterized by multiple tumors and hypergastrinemia (18-22). All of our five patients had type 1 tumors according to the classification of Rindi *et al.*, and have been followed-up without any distinct evidence of recurrence.

Surgical strategies against gastric carcinoids have been changing in the last decade. Hirschowitz *et al.* reported that multicentric ECL gastric carcinoids in patients with pernicious anemia and achlorhydria appear to be gastrin-dependent and disappear after normalization of the serum gastrin level by antrectomy (23). Antrectomy, rather than total gastrectomy, may be the most appropriate treatment for multicentric gastric carcinoids. Gilligan *et al.* have proposed a decision tree for the management of gastric carcinoid tumors (9). Type 3 sporadic lesions require aggressive surgical management on diagnosis. Type 1 and type 2 (hypergastrinemia-associated) lesions can be managed initially by endoscopic excision of accessible tumors, followed by endoscopic surveillance. If tumors recur, antrectomy and local excision may be used to remove the source gastrin. Previously, total gastrectomy was regarded as the treatment of choice because of the disease's unknown biological characteristics. Recent studies have reported that type 1 gastric carcinoids have a low potential for malignancy. Minor invasive surgery, such as endoscopic mucosal resection or laparoscopic antrectomy, has been performed for type 1 gastric carcinoids (24-27), but requires strict post-treatment surveillance. However, cases of multiple gastric carcinoids infrequently exhibit a re-increase of serum gastrin and/or

recurrence of carcinoids during post-operative follow-up. Our five patients underwent total gastrectomy and showed no recurrence during long-term observation. Therefore, gastrectomy should still be considered as one of the treatments for multiple gastric carcinoids with hypergastrinemia.

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