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【 CASE REPORT 】

Gastric Neuroendocrine Carcinoma with Rapid Progression

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Abstract:
As gastric neuroendocrine carcinoma (NEC) is a rapidly growing cancer, most cases are diagnosed at advanced stages. We herein report a 74-year-old woman with an early-stage gastric NEC whose history included endoscopic submucosal dissection treatment for three early-stage gastric cancer lesions five years prior to the current presentation. We also describe the changes observed over time. An endoscopic examination during follow-up revealed an NEC (measuring 6 mm) in the gastric vestibule, for which distal gastrectomy was performed. Four months before surgery, the carcinoma exhibited specific morphological changes and lymphovascular invasion (despite the tumor being stage 1), suggesting a high-grade NEC.

Key words: gastric neuroendocrine carcinoma, gastric cancer

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Introduction

Gastric neuroendocrine carcinoma (NEC) is a rare disease that accounts for 0.1-0.6% of all gastric cancers. It is a highly malignant tumor that exhibits features of rapid growth and has a high rate of metastasis and a poor prognosis (1, 2), with the grade of malignancy being much higher than that of gastric adenocarcinoma. The median survival times reportedly range from 7 to 46 months, with lymphatic and vascular invasion occurring in 73-92.3% and 76.9-81.5% of cases, respectively (2-7). Due to its rapid progression, NEC is rarely diagnosed at an early stage, and early-stage carcinoma cases are thus not commonly reported (4-15% of gastric NEC cases) (2, 5, 7).

We herein report a case with early-stage gastric NEC in which endoscopy was performed a total of four times prior to surgery, allowing morphological changes to be observed over time.

Case Report

The patient was a 74-year-old woman with diabetes and heart disease who had undergone endoscopic submucosal dissection (ESD) for 3 early-stage gastric cancer lesions 5 years prior to the current presentation. We performed curative resection of two pT1a lesions in the gastric vestibule. One lesion in the gastric corpus was a pT1a signet cell carcinoma that met the expanded indications and thus was curatively resected. The patient received treatment for *Helicobacter pylori* and regularly, i.e. every six months, underwent esophagogastroduodenoscopy (EGD). In addition, she was maintained on oral rabeprazole sodium (10 mg/day) for gastroesophageal reflux disease for five years.

A physical examination revealed no abnormalities, and her gastrin level was 220 pg/mL. EGD performed 11 months before surgery showed no abnormalities at the ESD scar site (Fig. 1A), but a small bulge (measuring 3 mm) near the scar site was recognized in the anterior wall of the lesser curvature of the gastric vestibule five months before surgery (Fig. 1B). On a biopsy, a histopathological examination revealed the epithelium to have a disorganized nuclear arrangement partially covering the gastric mucosa. Since the lesion was accompanied by intestinal metaplasia and invasion of inflammatory cells, it was diagnosed as group 2. The lesion stained negatively for synaptophysin and chromo-

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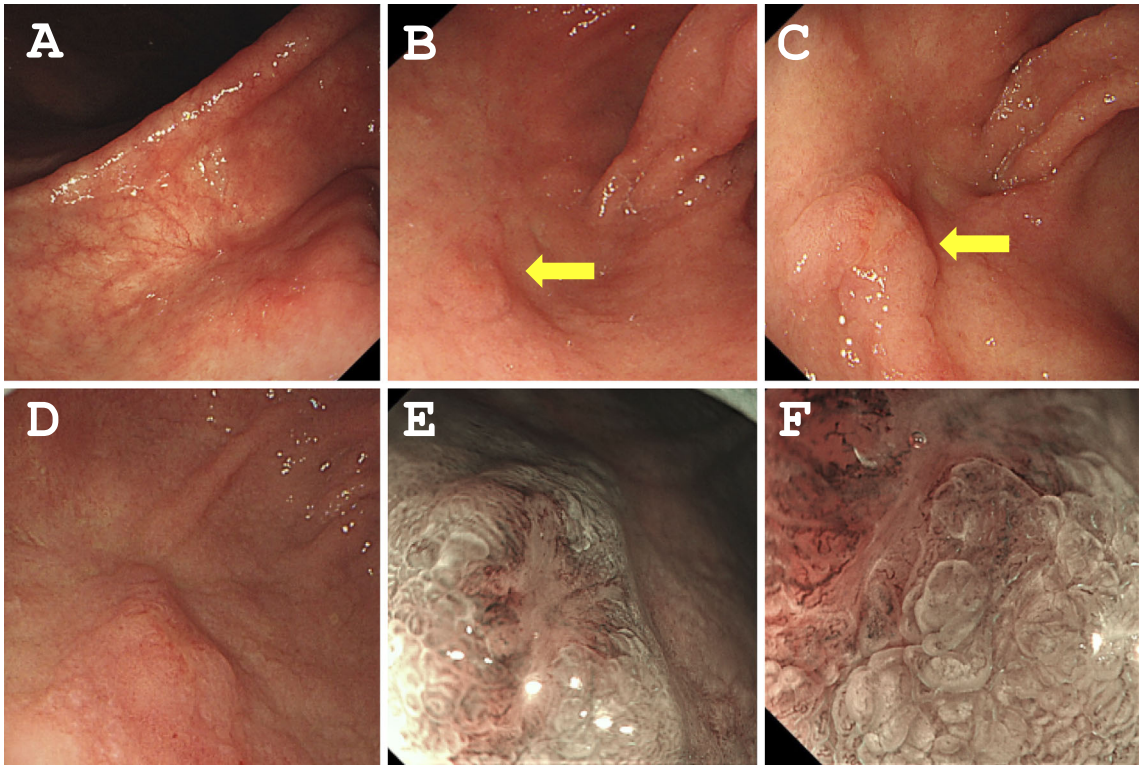

Figure 1. **(A) Eleven months before surgery, no abnormalities were seen in the mucosa of the ESD scar site in the anterior wall of the lesser curvature of the gastric pyloric vestibule. A biopsy of the scar revealed group 1. (B) Five months before surgery, a small bulge (measuring 3 mm) near the ESD scar site, close to the greater curvature (arrow), was seen. A biopsy of the site revealed group 2. (C) Two months before surgery, the mass near the ESD scar site in the anterior wall of the lesser curvature of the gastric vestibule was seen as a visibly protruding lesion (measuring 6 mm) with an excavation in the center (arrow). A biopsy of the site revealed an NEC. (D) One month before surgery, the NEC was found to have grown to 10 mm in size and changed into a swollen tumor-like lesion. (E) On NBI at low-power magnification, a line of demarcation matching the border of the excavation was observed. (F) On NBI at high-power magnification, irregularities in the internal surface structure and vascular structure were observed. ESD: endoscopic submucosal dissection, NBI: narrow-band imaging, NEC: neuroendocrine carcinoma**

granin A (Fig. 2A-D). EGD performed two months before surgery revealed a change, with the lesion having become the protruding type (measuring 6 mm), showing an excavation in the center, and a biopsy confirmed an NEC (Fig. 1C). Immunohistochemical staining with synaptophysin and chromogranin A yielded strongly positive results, with Ki-67-positive cells comprising over 80%, and there were no adenocarcinoma components. Based on the 2010 World Health Organization classification, we diagnosed this lesion as a gastric NEC (Fig. 2E-H) (8).

Computed tomography detected no metastases, and the clinical stage according to the International Union Against Cancer TMN classification was NEC, cT1N0M0, stage I (9). Because a thorough assessment of her ischemic heart disease was time-consuming, EGD was performed again one month before surgery, demonstrating a clear morphological change in the swollen submucosal tumor that had grown to over 10 mm in diameter (Fig. 1D-F).

Distal gastrectomy was performed two months after the diagnosis of NEC. A histopathological examination of the resected specimen showed medium-to-large atypical cells forming a large zellballen, with an accompanying pseudoglandular cavity-like structure. The cells stained positively for chromogranin A, synaptophysin, and CD56 (neural cell adhesion molecule), and the Ki-67 labeling index was over 80%. Although the muscularis mucosae was maintained, the tumor had invaded the submucosa in a miniaturized alveolar form. Venous invasion and multiple lymph vessel invasions were present, and the tumor had invaded up to a depth of 1,900 μm beyond the lower border of the muscularis mucosae. The histopathological result was 0-IIa, 11×10×3 mm, endocrine carcinoma, pT1b2 (SM2), int, INFb, ly2, v1, PM(−), DM(−), pP0, pH0, CY0, R0, lymph node metastasis (0/24), and stage I gastric cancer according to the International Union Against Cancer TMN classification (Fig. 3). There was neither a mucinous nor an adenocarcinoma component. We therefore diagnosed this patient with NEC without an adenocarcinomatous component (pure NEC).

Because lymphovascular invasion was present, meticulous follow-up examinations were performed, and the patient has

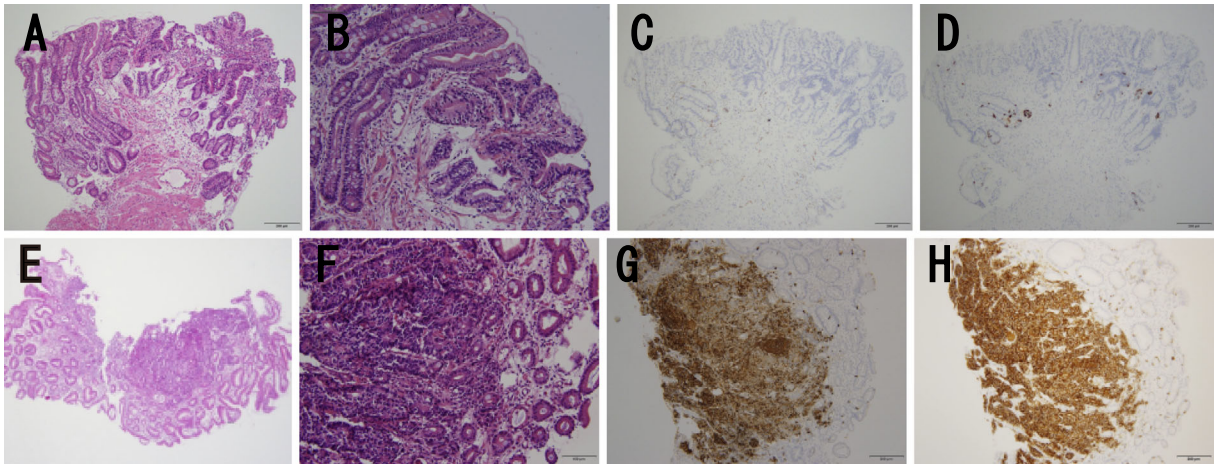

Figure 2. **(A) Five months before surgery: Hematoxylin and Eosin (H&E) staining ×10. (B) Five months before surgery: H&E staining ×20. (C) Five months before surgery: synaptophysin ×10. (D) Five months before surgery: chromogranin A ×10. (E) Two months before surgery: H&E staining ×4. (F) Two months before surgery: H&E staining ×20. (G) Two months before surgery: synaptophysin ×10 strong staining. (H) Two months before surgery: chromogranin A ×10. (A-D) Five months before surgery: A small bulge (measuring 3 mm) is observed. The gastric mucosa is partially covered by an epithelial layer showing a disorganized nuclear arrangement with accompanying intestinal metaplasia and invasion of inflammatory cells. Neither synaptophysin nor chromogranin A staining indicates NEC. The biopsy revealed group 2. (E-H) Two months before surgery: The lesion changed into a protruding type (measuring 6 mm) with a central excavation, and a biopsy of the site revealed an NEC of the epithelium. NEC: neuroendocrine carcinoma**

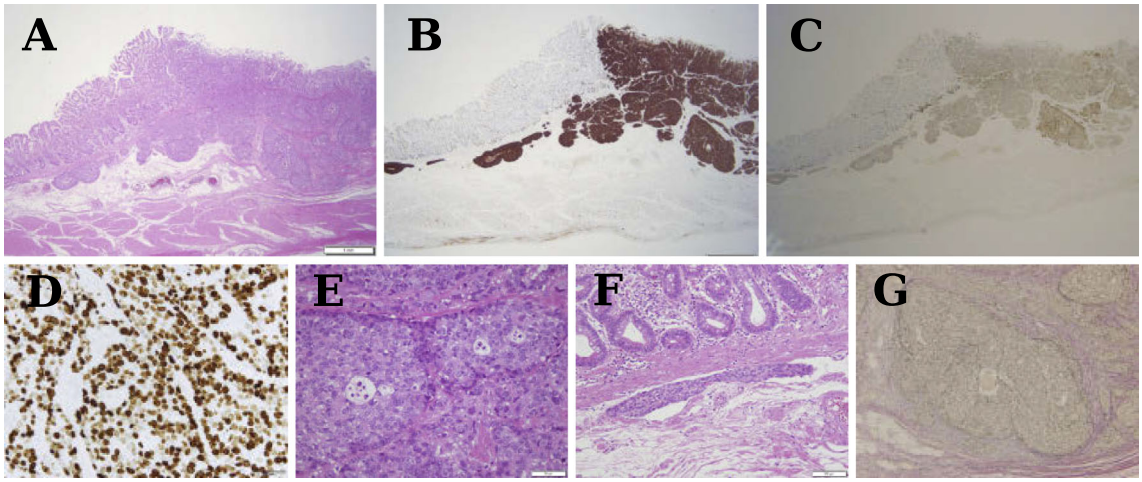

Figure 3. **(A) Hematoxylin and Eosin (H&E) staining ×2: Although the muscularis mucosae remains intact, tumor invasion into the submucosa is observed. (B) Synaptophysin ×2: Strong staining. (C) Chromogranin A ×2. (D) Ki-67 ×40: The Ki-67 labeling index is over 80%. (E) H&E staining ×40: A pseudogland accompanied by necrotic substances. (F) H&E staining ×20: Lymph vessel invasion is present. (G) EVG staining×10: Venous invasion is present. Medium-to-large atypical cells form a large zellballen, with an accompanying pseudoglandular cavity-like structure, and the cells are stained positive for chromogranin A, synaptophysin, and CD56 (neural cell adhesion molecule). Ki-67: ≥80%, SM: 1,900 μL. 0-IIa, 11×10×3 mm, endocrine carcinoma, pT1b2 (SM2), int, INFb, ly2, v1, PM (-), DM (-), pP0, pH0, CY0, R0, lymph node metastasis (0/24)**

remained recurrence- and metastasis-free for 18 months since the surgery.

Discussion

We experienced a case of gastric NEC subjected to endoscopy 4 times in total starting 11 months before surgery,

Table. Clinicopathologic Characteristics of the Seven NEC and MANEC Cases, with Detailed Descriptions, in the Literature.

No	Year	Reference	Age	Sex	Location	Size (mm)	Type	Histopathological diagnosis at biopsy	First treatment	Final histopathological diagnosis	Depth	Additional treatment	Turning point
1	1998	(12)	60	F	Body	20×15	Not stated	Adenocarcinoma	Gastrectomy	Adeno. NEC	SM	None	36 mo. survival
2	2013	(13)	67	M	Antrum	35×35	Not stated	Not stated	Gastrectomy	Pure NEC	SM2	None	8 mo. survival
3	2014	(14)	80	M	Body	10×9	0-IIc	Adenocarcinoma (moderate)	ESD	MiNEN	SM2	Gastrectomy	36 mo. survival
4	2015	(15)	77	M	Antrum	10×6	0-IIc	Adenocarcinoma (moderate)	ESD	MiNEN	M	None	7 mo. survival
5	2016	(16)	63	M	Angle	23×20	0-IIc	Adenocarcinoma (moderate)	Gastrectomy	MiNEN	SM2	Chemotherapy	16 mo. survival
6	2018	(17)	70	M	Antrum	17×9	0-IIc	Adenocarcinoma (well)	ESD	MiNEN	SM1	Gastrectomy and chemotherapy	50 mo. survival
7	2019	Our case	74	F	Antrum	11×10	0-IIa+IIc	Pure NEC	Gastrectomy	Pure NEC	SM2	None	18 mo. survival

Results were obtained with a PubMed search (cases between 1998–2018).

SM: submucosa, Adenocarcinoma (moderately): moderately differentiated tubular adenocarcinoma, Adenocarcinoma (well): well-differentiated tubular adenocarcinoma, Adeno.: adenocarcinoma, Pure NEC: NEC without an adenocarcinomatous component, MiNEN: mixed neuroendocrine-non-neuroendocrine neoplasm

which enabled us to observe the characteristic morphological changes over time. The 6-mm lesion was initially found at what appeared to be an early stage; however, a histopathological examination of the surgical specimen revealed submucosal invasion, lymph vessel invasion, and vascular invasion.

Although gastric NEC is a relatively rare disease, the degree of malignancy is high, and this tumor is commonly diagnosed in the advanced stage and/or with multi-organ metastases. Thus, only a small number of cases are diagnosed in the early stages. Ishida et al. (2) reported that of 7,886 cases undergoing surgical resection for gastric cancer, 51 (0.64%) had gastric NEC, among which there were no cases with early-stage T1a cancer and only 2 (4%) with T1b tumors. Matsui et al. (7) identified 1 case (8%) with T1b disease among 33 gastric NEC cases, and Kubota et al. (5) identified 4 T1 cases (15%) among 27 gastric NEC cases.

Currently, pancreatic and gastrointestinal neuroendocrine tumors are collectively referred to as neuroendocrine neoplasm (NEN). In the World Health Organization (WHO) 2010 guidelines, a classification using the Ki-67 index and nuclear division, which are predictive of proliferation, was created. This classification allowed NEN to be broadly divided into neuroendocrine tumor (NET) and NEC. Later, the WHO 2017/2019 classifications were revised while taking into account the degree of differentiation. Tumors that show histologic neuroendocrine patterns are presently referred to as highly differentiated, and the Ki-67 index categories are < 3%, 3-20%, and >20%; based on these determinations, the tumors are classified as NET G1, G2, and G3, respectively, and morphologically poorly differentiated neuroendocrine tumors with a Ki-67 index exceeding 20% are defined as NEC. In addition, NEC is known to frequently coexist with adenocarcinoma. WHO 2010 proposed a classification of mixed adenoneuroendocrine carcinoma (MANEC) based on the ratio in tumors comprising both NEC and adenocarcinoma. However, the WHO 2019 classification revised the description of epithelial tumors with a mixture of non-neuroendocrine and neuroendocrine components, now identifying them as mixed neuroendocrine-non-neuroendocrine neoplasm (MiNEN) (10, 11).

Domori et al. (6) assessed 52 gastric NEC cases and reported 39 (75%) with NEC that had an adenocarcinomatous component (Adeno NEC), whereas Ishida et al. (2) reported a proportion of 71%. In Japan, where gastric adenocarcinoma is common, Adeno NEC, including MANEC, tends to be more common than in western countries (2, 6). However, case reports describing the diagnosis at an early stage are rare. Mainly cases diagnosed as MANEC after ESD and additional surgery and those diagnosed as NEC from a metastatic lesion following ESD have been reported (12-17). A search of PubMed for case reports (between 1998 and 2018) of gastric NEC diagnosed at early stages yielded only seven cases, including ours, in which the patient age, sex, site of occurrence, and depth of invasion could be assessed in detail (Table) (12-17). Most cases had been diagnosed as having adenocarcinoma based on a biopsy obtained before the first treatment, and those diagnosed with NEC by a biopsy were extremely rare.

In MANEC, highly proliferating neoplastic neuroendocrine cells develop into tubular adenocarcinoma, and NEC components are commonly localized in the deepest site of the tumor. Furthermore, since NEC components are mainly located deep in the mucosal layer while the surface layer of the NEC is covered by non-tumorous mucosa or adenocarcinoma, a diagnosis based on a biopsy alone before total resection of the tumor is considered difficult (14, 15).

We found that periodic endoscopy after ESD contributed

to the early detection of NEC in our present patient. Furthermore, a preoperative biopsy was able to be performed because the tumor was exposed on the concave surface of the apex and there was no adenocarcinoma component.

Gastrointestinal endocrine cells are widely distributed and interspersed among other epithelial cells. In the pyloric vestibule, G cells secreting gastrin are present in the neck region of the glands. Regarding the mechanism underlying gastric NET development, as in Rindi classification type 1, a pathway leading from the hyperplasia of G cells in the gastric vestibule to hyperplasia of enterochromaffin-like (ECL) cells due to hypergastrinemia to the tumor has been proposed. However, such a mechanism has not been reported in gastric NEC (18, 19).

Even in the present case, the NEC that developed in the gastric vestibule was suspected to be associated with high gastrin levels due to long-term oral proton pump inhibitor therapy. However, since the patient's gastrin levels were not found to be elevated (220 pg/mL), a clear relationship between these two factors could not be established.

In the case of MANEC, the mechanism underlying the formation of an endocrine carcinoma within a preceding adenocarcinoma has been inferred (6). Given that ESD had been performed in the present case for well-differentiated adenocarcinoma in the pylorus five years prior to the current presentation and that the site of development was close to the scar site, a histological relationship was suspected. However, no adenocarcinoma components were detected in either the tissue specimens from the three biopsies performed or the surgical specimen. Therefore, we considered the lesion to be a pure NEC that had developed independently.

Because of the increase in the number of endoscopic examinations and advances in diagnostic methods, the incidence and prevalence of gastric NET have increased. The incidence of gastric neuroendocrine tumors, including NET and NEC, has reportedly ranged from 0.19-0.46 per 100,000 population in recent years (20-22). During the past 10 years, Hauso et al. (21) reported that the incidence had increased by 39% and 88% in Norway and United States, respectively. Furthermore, a survey conducted in the Netherlands between 1990 and 2010 showed that the 5-year survival rate had decreased from 7% to 3% for gastric small-cell NEC, indicating that the prognosis of gastric NEC remains poor (20).

There are clinical guidelines recommending treatment strategies for locally advanced NEC, including chemotherapy and radiotherapy but not surgical resection. In the event of surgical resection being selected, the authors recommended adjuvant platinum-based chemotherapy as well (23, 24). Since our patient had stage I disease, however, and was elderly with an underlying disease, we opted not to administer postoperative adjuvant chemotherapy. Even though clinical stage 1 is an indication for surgical monotherapy with most forms of gastric cancer, a treatment policy with adjuvant chemotherapy should be considered among the options for NEC.

Although the lesion was very small in the present case, it was a pure NEC that exhibited a high Ki-67 index and specific changes during growth from a small lesion measuring only 3 mm to a swollen submucosal lesion measuring 10 mm over a period of 4 months. It showed a strong tendency for submucosal progression from the early stage of development. In addition, lymph vessel invasion and vascular invasion were observed in the surgical specimen. We were therefore able to further confirm rapid tumor invasion based on the histopathological findings.

Gastric NEC has a high grade of malignancy and advances rapidly. Therefore, while adjuvant chemotherapy options should be explored, surgical treatment needs to be performed as soon as possible after discovery, even for small lesions.

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

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