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## Case of gastric neuroendocrine carcinoma showing an interesting tumorigenic pathway

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### Abstract

Here, we report a case of gastric neuroendocrine carcinoma showing an interesting tumorigenic pathway. A 57-year-old Japanese woman presented with epigastric tenderness, and distal gastrectomy was performed. In the surgical specimen, histologically, the tumor tissue was composed of three subtypes of tumor components showing different histological architecture and cellular atypia, diagnosed as neuroendocrine tumor (NET) G2, NET G3, and neuroendocrine carcinoma (NEC) components. Immunohistochemically, the Ki-67-positive rates of NET G2, NET G3, and NEC components were 6.5%, 99.5% and 88.1%, respectively. Although allelic imbalance (AI) on chromosomes 1p, 3p, 8q, TP53, 18q and 22q was commonly found in all components, AI of 4p was found in NET G3 and NEC components (but not in the NET G2 component). In contrast, AIs of 5q and 9p were found in only the NEC

component. Thus, we showed the progression from NET G2 to NEC, via NET G3, within the same tumor.

**Key words:** Stomach; Neuroendocrine tumor G2; Neuroendocrine tumor G3; Neuroendocrine carcinoma

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**Core tip:** Gastric neuroendocrine carcinoma (NEC) is typically generated by dedifferentiation of adenocarcinoma cells to endocrine cells. However, we experienced a case of gastric NEC possibly generated from the neuroendocrine tumor (NET) component. The present case demonstrated an unconventional carcinogenic pathway in neuroendocrine tumorigenesis. In addition, we analyzed allelic imbalance in NET and NEC components and provided important insights into neuroendocrine carcinogenesis.

Uesugi N, Sugimoto R, Eizuka M, Fujita Y, Osakabe M, Koeda K, Kosaka T, Yanai S, Ishida K, Sasaki A, Matsumoto T, Sugai T. Case of gastric neuroendocrine carcinoma showing an interesting tumorigenic pathway. *World J Clin Cases* 2017; 5(11): 397-402 Available from: URL: <http://www.wjgnet.com/2307-8960/full/v5/i11/397.htm> DOI: <http://dx.doi.org/10.12998/wjcc.v5.i11.397>

## INTRODUCTION

Neuroendocrine neoplasms of the digestive system are classified as neuroendocrine tumors (NETs) or neuroendocrine carcinomas (NECs) based on assessment of the pro-liferative fraction and morphological criteria in the 2010 World Health Organization (WHO) classification. Furthermore, NET can be divided into three tiers (G1, G2, and G3) based on the mitotic count and Ki-67 labeling index<sup>[1]</sup>. NEC of the stomach is composed of proliferation of poorly differentiated tumorous endocrine cells with marked cellular atypia<sup>[1]</sup>. In general, gastric NEC may be generated by dedifferentiation of adenocarcinoma cells to endocrine cells, and it is possible that gastric NETs and NECs may have different tumorigenic pathways<sup>[1,2]</sup>. Here, we report a case of gastric NEC generated from a NET component, with immunohistochemical and molecular studies.

## CASE REPORT

A 57-year-old Japanese woman presented with epigastric tenderness. Gastroendoscopy showed a growing lesion (size, 16 mm × 11 mm) in the greater curvature of the upper gastric body, and the mucosa adjacent to the lesion showed atrophic gastritis. Histopathological examination of a biopsy sample revealed NEC. *Helicobacter pylori* were not detected

by Giemsa staining. In addition, serum levels of chromogranin A and gastrin were not measured. The patient subsequently underwent distal gastrectomy. One year after surgery, liver metastasis was found in abdominal computed tomography examination, and chemotherapy was performed.

## Pathological findings

In low-magnification images, tumor cells were distributed in two lesions. One lesion was constructed by tumor cell proliferation within the submucosal layer, and another lesion was found in the muscle layer; these two lesions were discontinuous (Figure 1A).

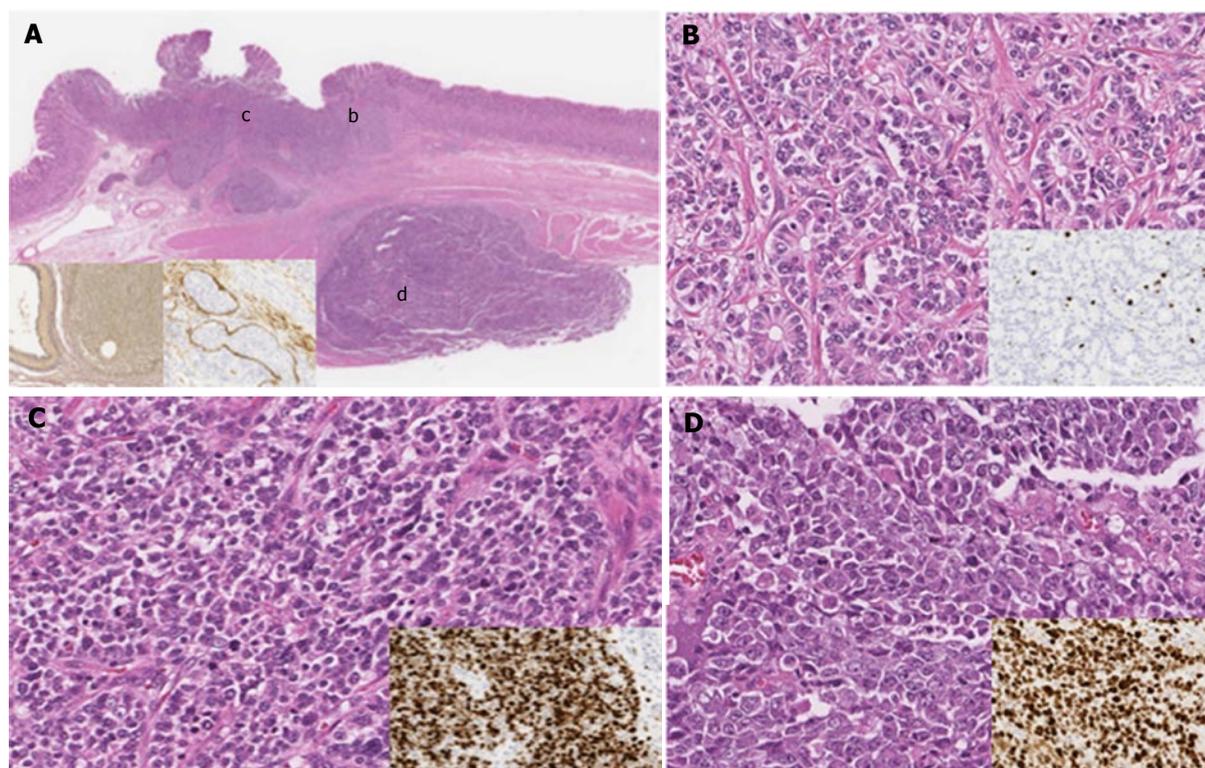
Microscopic examination revealed that the tumor tissue was composed of three subtypes of tumor components as follows. The first component was composed of cuboidal epithelial cells with uniform, oval nuclei showing fine nuclear chromatin and arranged in a trabecular growth pattern with focal rosettes. Tumor cells had very few mitotic figures [ $< 2$  per 10 high-powered fields (HPF)] and no necrosis. This component corresponded to the NET G2 component (Figure 1B). The second component consisted of diffuse proliferation of tumor cells with small nuclei showing irregular, dense nuclear chromatin and high mitotic counts, corresponding to the NET G3 component (Figure 1C). The third component was composed of diffuse proliferation of tumor cells with large, irregular, coarse nuclei, high mitotic counts, and geographic necrosis, similar to the large cell NEC component (Figure 1D). Although the transition between the NET G2 component and the NET G3 component was confirmed, the submucosal lesion and intramuscular lesion were separated by the muscle layer (Figure 1A). Marked lymph vessel and venous invasion were observed in the submucosal layer, as determined by D2-40 immunohistochemical staining and EVG staining (Figure 1A, inset).

In addition, the mucosa adjacent to the tumor showed atrophic gastritis with intestinal metaplasia, but not type A gastritis. No endocrine cell micronests were found in the surrounding mucosa.

## Immunohistochemical study

Immunohistochemical examination was performed using an auto-immunostaining system (Dako EnVision System, Denmark) for neuroendocrine differentiation, cell proliferation activity, p53 overexpression, and mucin phenotype (Muc2, Muc5AC, Muc6, CD10). The positive rate of Ki-67 was calculated using an APERIO virtual slide system (AT2; Leica Biosystems, United States).

All tumor components were immunopositive for chromogranin A, synaptophysin, and CD56, and decreased immunoreactivity was found in the NEC component. Differences in Ki-67-positive rates were



**Figure 1** Histological findings of an HE-stained section of a resected specimen. A: Low-magnification image of the surgical specimen. The tumor component was composed of two lesions (a submucosal lesion and an intramucosal lesion). These two lesions were separated by muscle layer (inset: left, EVG staining; right, D2-40 immunohistochemical staining); B: NET G2 component (inset: Ki-67 positive rate, 6.5%); C: NET G3 component (inset: Ki-67 positive rate, 99.5%); D: Large cell NEC component (inset: Ki-67 positive rate, 88.1%). NEC: Neuroendocrine carcinoma; NET: Neuroendocrine tumor.

found among NET G2, NET G3, and NEC components (NET G2, 6.5%; NET G3, 99.5%; NEC, 88.1%). Overexpression of p53 protein was not found in any component. With regard to the mucin phenotype, no mucin markers were expressed in any tumor component (Table 1).

### Molecular findings

DNA from NET G2, NET G3, and NEC components was extracted separately. PCR-allelic imbalance (AI) analyses were performed using a thermal cycler (GeneAmp PCR System 9600; Perkin-Elmer, CA, United States) according to previously reported procedures<sup>[3]</sup>. AIs on chromosomes 1p, 3p, 4p, 5q, 8p, 9p, 13q, 17p, 18p, and 22q were examined using 22 highly pleomorphic microsatellite markers (D1S228, D1S548, D3S2402, D3S1234, D4S2639, D4S1601, D5S107, D5S346, D5S299, D5S82, D8S201, D8S513, D8S532, D9S171, D9S1118, D13S162, TP53, D18S487, D18S34, D22S274, D22S1140, and D22S1168).

In addition, PCR-MSI analysis was performed as described previously<sup>[4]</sup>. Five different loci were assessed for MSI, including all those recommended by the Bethesda panel for colon cancer (BAT25, BAT26, D5S346, D2S123, and D17S250)<sup>[4]</sup>.

DNA methylation at the six specific promoters originally described by Yagi and colleagues was

quantified<sup>[5]</sup>. Methylation of three markers (RUNX3, MINT31, and LOX) was analyzed, and samples with at least two methylated markers were defined as highly methylated epigenotype (HME) tumors. The remaining tumors were also screened for methylation at three other markers (NEUROG1, ELMO1, and THBD) and were defined as intermediate methylation epigenotype (IME) tumors if they had at least two methylated markers out of the three markers proposed as a second panel. Tumors not classified as HME or IME were designated as low methylation epigenotype (LME).

In the present case, DNA methylation status was LME, and MSI was not found in all tumor components. AIs at 1p, 3p, 8q, TP53, 18q and 22q were commonly found in all tumor components. Although AI of 4p was found in NET G3 and NEC components, it was not observed in the NET G2 component. In addition, AIs at 5q and 9p were found in the NEC component only (negative for NET G2 and G3 components; Figure 2).

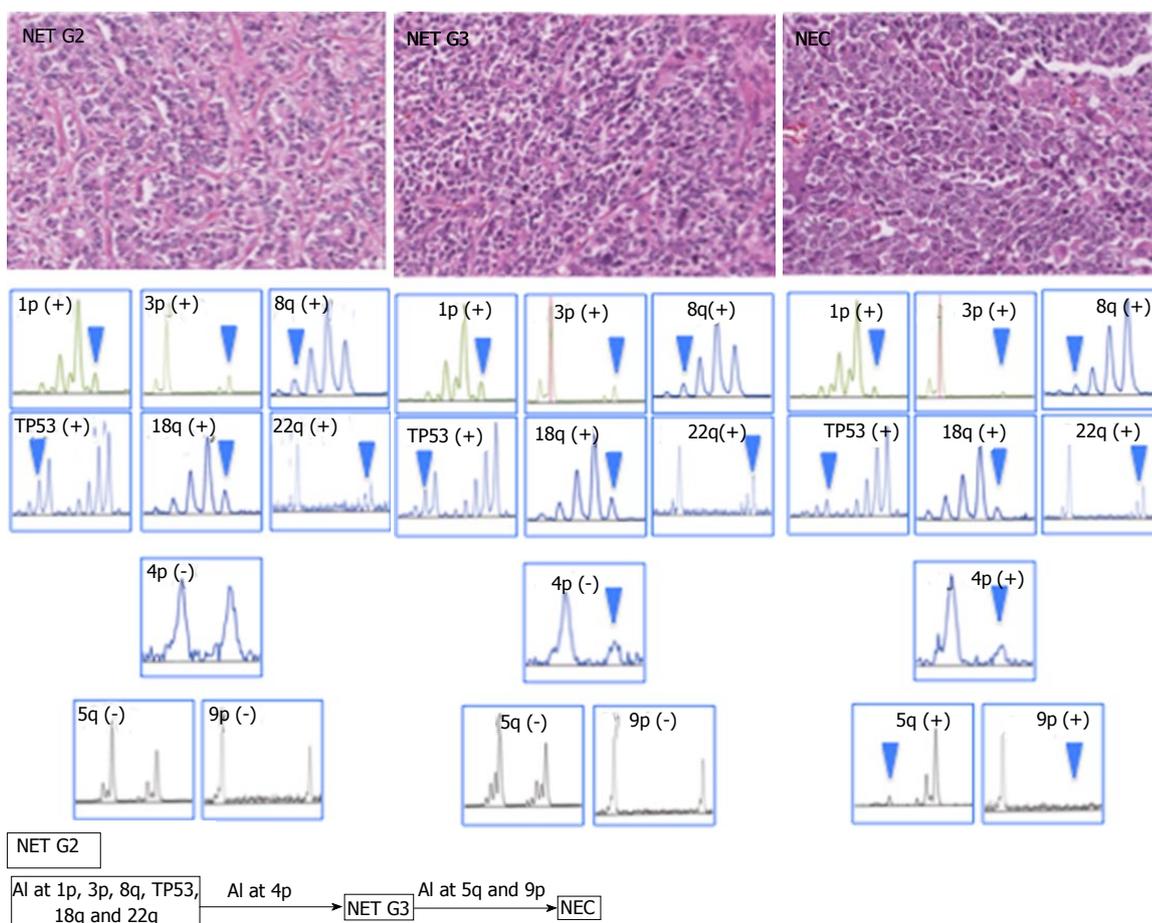
## DISCUSSION

Most cases of gastric NEC may be developed from endocrine precursor cell clones occurring in preceding adenocarcinoma components<sup>[1,2]</sup>. In the present case, histological examination revealed that the tumor

**Table 1 Summary of immunohistochemical analysis**

Antibody	Clone	Dilution	Source	NET G2 component	NET G3 component	NEC component
Chromogranin A	DAK-A3	1:100	DAKO, CA, Unites States	Positive	Positive	Weakly positive
Synaptophysin	SY38	1:20	DAKO, CA, Unites States	Positive	Positive	Weakly positive
NCAM	1B6	1:100	DAKO, CA, Unites States	Positive	Positive	Weakly positive
Ki-67	MIB-1	1:50	DAKO, CA, Unites States	6.50%	99.50%	88.10%
p53	DO-7	1:100	Novocastra, United Kingdom	Negative	Negative	Negative
Muc2	Ccp58	1:200	Novocastra, United Kingdom	Negative	Negative	Negative
Muc5AC	CLH2	1:100	Novocastra, United Kingdom	Negative	Negative	Negative
Muc6	CLH5	1:100	Novocastra, United Kingdom	Negative	Negative	Negative
CD10	56C6	1:50	Novocastra, United Kingdom	Negative	Negative	Negative

NEC: Neuroendocrine carcinoma.



**Figure 2 Accumulation of allelic imbalance through the progression from neuroendocrine tumor G2 to neuroendocrine tumor G3 to neuroendocrine carcinoma in the present case.** AIs at 1p, 3p, 8q, TP53, 18q, and 22q were common in three components (NET G2, NET G3, and NEC). AI at 4p was acquired during the progression from NET G2 to G3. AIs at 5q and 8q were found during progression from NET G3 to NEC. NEC: Neuroendocrine carcinoma; NET: Neuroendocrine tumor; AI: Allelic imbalance.

tissue was composed of three subtype components. In addition, the transition between NET G2 and G3

components was confirmed. No adenocarcinoma components were found in serial sections of all specimens. Although a clear transition between the NET and NEC components was not found, we assumed that the tumor mass in the muscle layer may be an intramural metastasis because the tumor tissue showed marked vessel invasion (Figure 1A). Therefore, we speculated that the morphological change from NET to NEC could have occurred through the process of tumor progression. Additionally, NEC may arise from the NET component, suggesting that the tumor may have developed through an unconventional pathway in neuroendocrine tumorigenesis in our case<sup>[2]</sup>.

With regard to the tumorigenesis of the NET G2 component, although serum chromogranin A and gastrin had been measured, no endocrine cell micronests or findings of type A gastritis were observed in the mucosa adjacent to the tumor. Therefore, we assumed that the tumor in this case may be sporadic NET, namely non-endochromaffin-like cell tumor, defined as type 3 tumor by Rindi *et al.*<sup>[1]</sup>.

In previous reports, most cases of gastric NEC with an adenocarcinomatous component were found to exhibit immunopositivity of mucin markers, and the mucin phenotype of the NEC component was found to correspond with that of the adenocarcinoma component<sup>[2,6]</sup>. In our case, both the NET and NEC components showed negative immunoreactivity for all mucin markers examined. Thus, it was unlikely that the NEC component was generated from adenocarcinoma in the present case.

Furthermore, Nishikura *et al.*<sup>[7]</sup> reported that most cases of NEC with an adenocarcinoma component showed p53 mutations, consistent with the adenocarcinoma component. This finding strongly supported the hypothesis that most cases of gastric NEC are developed from precursor cell clones that occur in a preceding adenocarcinoma component.

The molecular features of NET and NEC have not been clarified<sup>[8]</sup>. In the present case, AIs at 1p, 3p, 8q, TP53, 18q, and 22q were commonly found in three components (NET G2, NET G3, and NEC). These findings supported that the tumor in our case had been generated by progression from the NET G2 to NEC component. In contrast, AI at 4p was acquired during the progression from NET G2 to G3. In addition, AIs at 5q and 8q play an important role in the development from NET G3 to NEC. These findings suggested that acquisition of multiple AIs contributed to the progression from NET to NEC (Figure 2).

In conclusion, we experienced a case of gastric NEC possibly generated from the NET component. The present case demonstrated an unconventional carcinogenic pathway in neuroendocrine tumorigenesis, providing important insights into neuroendocrine carcinogenesis.

## COMMENTS

### Case characteristics

Gastric neuroendocrine carcinoma showing unconventional tumorigenic pathway.

### Clinical diagnosis

Gastric carcinoma

### Laboratory diagnosis

Gastric carcinoma.

### Imaging diagnosis

Gastric carcinoma.

### Pathological diagnosis

Gastric neuroendocrine carcinoma

### Treatment

Distal gastrectomy

### Peer-review

This is an interesting case of gastric neuroendocrine carcinoma showing a tumorigenic pathway. This report presents a case of gastric NEC possibly generated from NET component by analyzing allelic imbalance and shows unconventional carcinogenic pathway in neuroendocrine tumorigenesis.

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