

[CASE REPORT]

Complete Remission with Nivolumab Monotherapy of Advanced Gastric Neuroendocrine Carcinoma

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Abstract:

A 77-year-old man with large-cell gastric neuroendocrine carcinoma underwent palliative total gastrectomy after 10 cycles of carboplatin and etoposide chemotherapy for severe tumor bleeding. Despite a histological grade 0 therapeutic effect, the remnant lesions were treated with paclitaxel and ramucirumab, but progression occurred after two cycles. Nivolumab monotherapy was then initiated, resulting in complete remission after three cycles. Nivolumab was discontinued because of immune-related psoriasis, but complete remission persisted for at least 16 months. This is the first reported case of nivolumab monotherapy achieving complete remission in gastric neuroendocrine carcinoma with the patient surviving 28 months.

Key words: nivolumab, neuroendocrine carcinoma, gastric cancer, paclitaxel, ramucirumab, carboplatin

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Introduction

Extrapulmonary neuroendocrine carcinoma (NEC) may develop in the gastrointestinal tract, especially in the esophagus, but rarely does it develop in the stomach. Gastric NEC accounts for only 7% of gastrointestinal NEC and 0.6% of gastric cancers, and its prognosis is poor (1-4). Platinum-based drugs with etoposide or irinotecan combination therapy are reportedly effective as first-line treatment (3, 5, 6), but no further effective line regimen for refractory cases has been reported.

In 2017, the survival benefits of nivolumab, a fully humanized IgG4 antibody to programmed cell death 1, were reported in large, randomized trials (7, 8) for the treatment of heavily pretreated patients with advanced gastric or gastroesophageal junction cancer. Since then, the cost of nivolumab has been covered by national insurance for unresectable or recurrent human epidermal growth factor receptor 2-negative gastric cancer in Japan. Although nivolumab has also been used to treat gastric NEC (9-11), its efficacy against gastric NEC has not been established.

We herein report a case of advanced gastric NEC that was

successfully treated with nivolumab monotherapy.

Case Report

A 77-year-old man underwent esophagogastroduodenoscopy for the evaluation of anemia with Hb 12.1 g/dL. The laboratory findings are presented in Table. The tumor markers CEA and CA19-9 were within the normal range, but NSE was elevated to 31.4 ng/mL (Table). Endoscopy revealed a large ulcerative lesion along the lesser curve extending from the gastric cardia to the antrum (Fig. 1a, b), a 15-mm slightly elevated lesion on the left side of the hypopharyngeal pyriform sinus (Fig. 1c, d), and a 5-mm reddish flat elevated lesion in the middle of the esophagus (Fig. 1e, f). Magnifying endoscopy with narrow-band imaging of the hypopharyngeal and esophageal lesions revealed dilated, distorted intraepithelial papillary capillary loops (Fig. 1d, f); based in these findings as well as those of biopsy specimens, the diagnosis of squamous cell carcinoma was made.

The histology of the gastric biopsy specimens was compatible with gastric NEC, i.e. atypical cells, characterized by densely stained enlarged nuclei and acidic cytoplasm, with

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infiltrative proliferation in a nest-like structure with positive immunostaining for synaptophysin, chromogranin, and CD 56 (Fig. 2). The tumor was negative for programmed cell death ligand 1 (PD-L1) (combined positive score <5), microsatellite instability, and human epidermal growth factor receptor 2. Contrast-enhanced computed tomography (CT) revealed irregular wall thickening throughout the stomach (Fig. 3a), direct tumor invasion into the liver and abdominal wall (Fig. 3a, b), and bulky lymph node metastasis in the lesser curve of the stomach (Fig. 3c). The TNM clinical

stage was Stage IVA with T4bN+M0 (12).

Because the patient was elderly and lived far from our hospital, we initiated treatment with a 60% dose of carboplatin and etoposide because of safety concerns. The treatment resulted in stable disease after 10 cycles without NSE elevation (Fig. 3d, 7). However, severe anemia due to gastric tumor bleeding progressed, and palliative total gastrectomy was performed. The pathological diagnosis of the resected specimen was large-cell NEC (Fig. 4): tumor size 130 mm, pT4b (SI), pP1 (positive peritoneal metastasis), R2 (macroscopic residual tumor), and pStage IV (12). No adenocarcinoma was noted in the study area, but the entire tissue was not evaluated in detail; therefore, the presence of adenocarcinoma components could not be ruled out. A histological assessment of the therapeutic response was grade 0 (no response). In the cancer profiling test (FoundationOne® CDx) of the resected specimens, the tumor mutation burden was low (8 mutations/megabase), and significant therapeutic mutations were detected.

On CT performed after surgery, remnant lesions were present on the anterior side of the pancreas and peritoneum (Fig. 5a, b). Weekly paclitaxel with ramucirumab was started as a second-line regimen for the treatment of the remnant lesions (13), but the disease progressed after two cycles (Fig. 5c, d); therefore, we started nivolumab as a third-line regimen, 480 mg once every 4 weeks. Complete remission was achieved after three cycles of nivolumab (Fig. 5e, f); however, therapy had to be discontinued because psoriasis, presumably due to an immune-related reaction, occurred. Complete remission continued 4 months after nivolumab was stopped, as documented by dynamic CT

Table. Laboratory Findings at the First Visit.

Biochemistry		Hematology	
TP	5.7 g/dL	WBC	$6.0 \times 10^3 / \mu\text{L}$
Alb	2.8 g/dL	Neu	67.9 %
ChE	143 U/L	Eo	1.8 %
CRP	4.71 mg/dL	Ba	0.2 %
T-bil	0.3 mg/dL	Mo	6.8 %
AST	11 U/L	Ly	23.3 %
ALT	8 U/L	RBC	$3.86 \times 10^6 / \mu\text{L}$
LDH	169 U/L	Hb	9.3 g/dL
ALP	339 U/L	Ht	31.3 %
γ -GTP	33 U/L	MCV	81.1 fL
UA	4.3 mg/dL	MCH	24.1 pg
BUN	18 mg/dL	MCHC	29.7 %
Na	141 mmol/L	Plt	$35.7 \times 10^4 / \mu\text{L}$
K	4.1 mmol/L	Tumor marker	
Cl	105 mmol/L	CEA	2.5 ng/mL
Ca	8.5 mmol/L	CA19-9	5.6 U/mL
Cre	0.7 mg/dL	NSE	31.4 ng/mL
eGFR	82.4 mL/min/1.73 m ²		

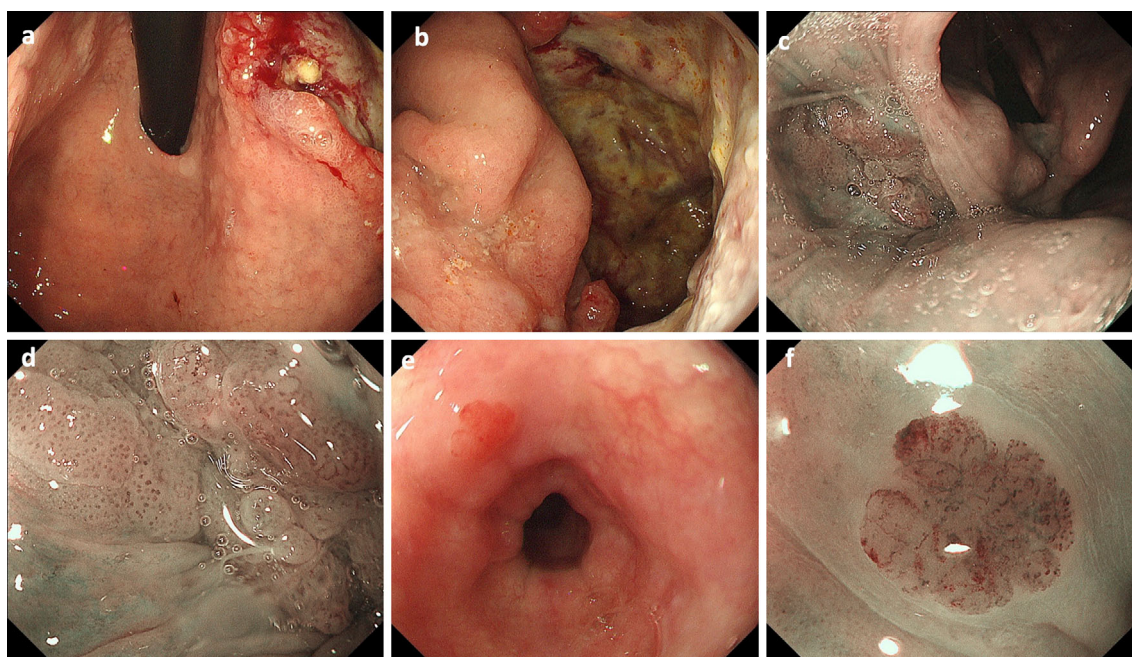


Figure 1. Endoscopic images of the lesions at the diagnosis. Large ulcerative lesion extending from the lesser curve of the gastric cardia (a) to the antrum (b). A 15-mm, slightly elevated lesion on the left side of the hypopharyngeal pyriform sinus (c, d). A 5-mm reddish flat elevated lesion in the middle of the esophagus (e, f). a, b, e: White-light images. c, d, f: Narrow-band imaging.

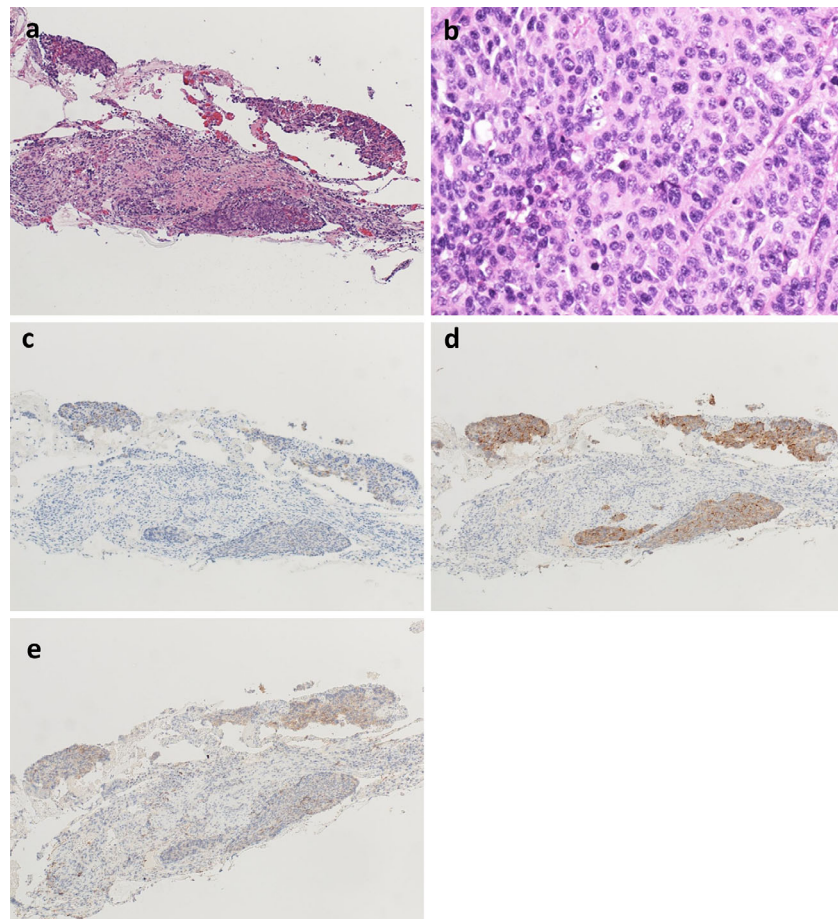


Figure 2. Pathological findings of biopsy specimens from the gastric lesion. Hematoxylin and Eosin staining (a). There is focal, dense proliferation of tumor cells with large round nuclei containing well-defined nucleoli (b). Immunostaining with chromogranin A (c), synaptophysin (d), and CD56 (e).



Figure 3. Contrast-enhanced CT images through the treatment course before palliative gastrectomy. CT images at the diagnosis (a, b, c) and after 10 cycles of carboplatin and etoposide chemotherapy (d). CT: computed tomography

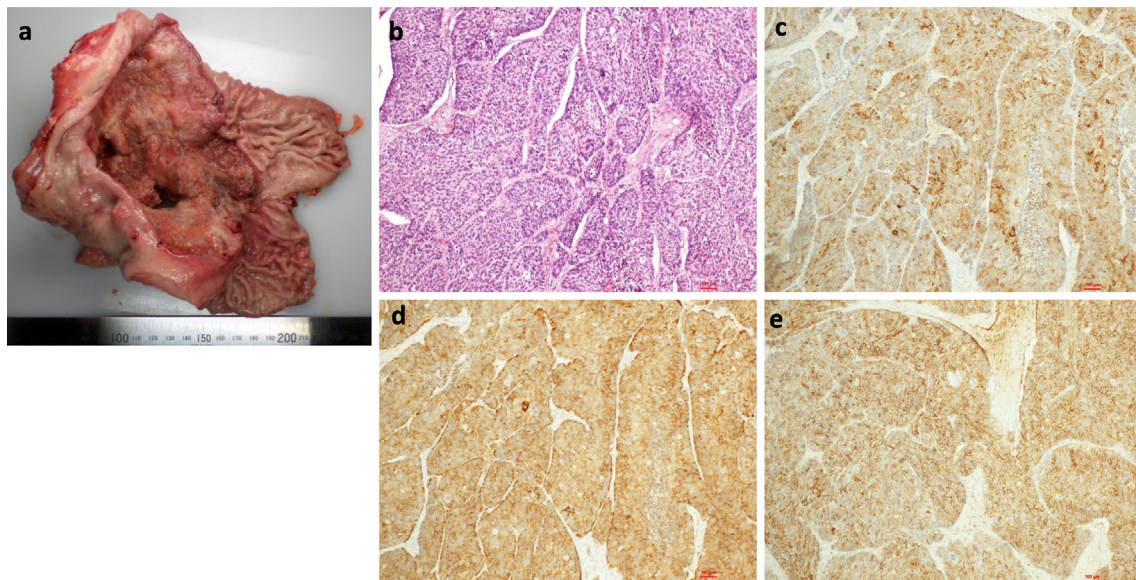


Figure 4. Pathological findings of the surgically resected specimen. Gross appearance of the resected gastric lesion (a). Hematoxylin and Eosin staining (b). Immunostaining with chromogranin A (c), synaptophysin (d), and CD56 (e).



Figure 5. Contrast-enhanced CT images throughout the treatment course after palliative gastrectomy. CT images after palliative resection of the gastric lesion (a, b), after two cycles of paclitaxel with ramucirumab (c, d), and after three cycles of nivolumab (e, f). Arrows indicate remnant lesions on the anterior side of the pancreas (a, c) and the peritoneum (b, d). CT: computed tomography

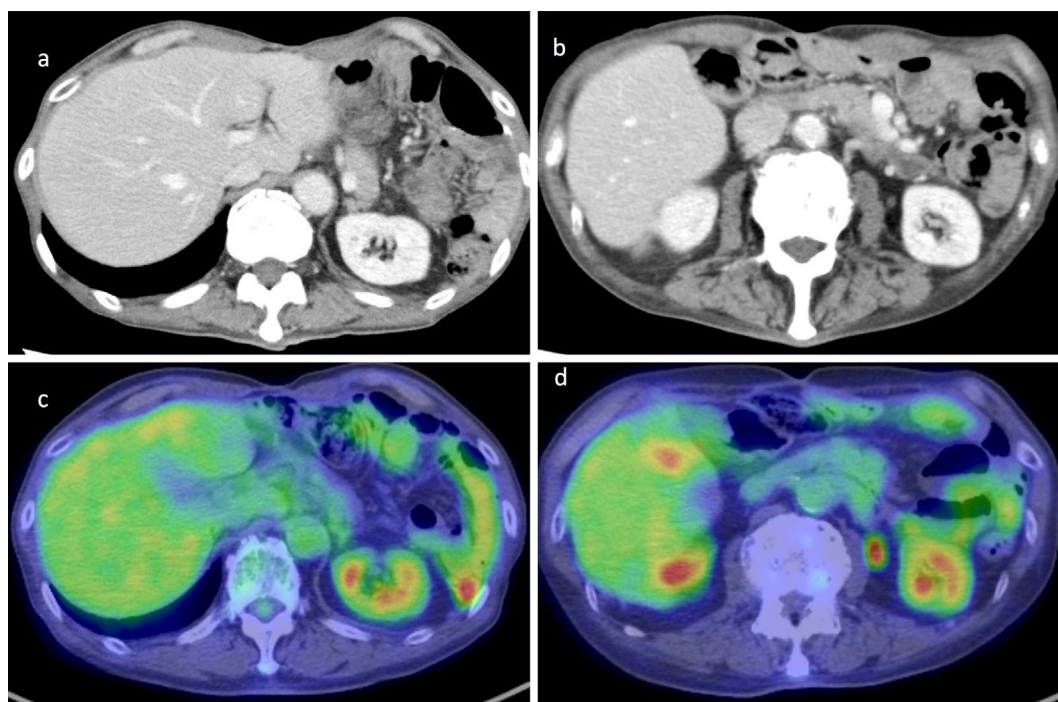


Figure 6. Images after stopping nivolumab. Contrast-enhanced CT images 4 months after discontinuation of nivolumab (a, b) and ^{18}F fluoro-2-deoxyglucose positron emission tomography images 16 months after discontinuation of nivolumab (c, d). CT: computed tomography

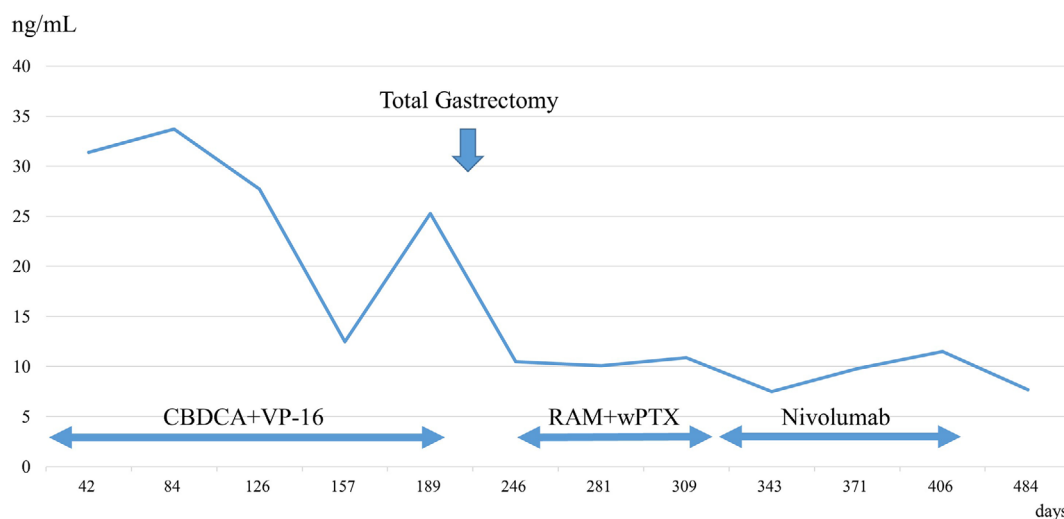


Figure 7. Changes in NSE over time. CBDCA+VP-16, carboplatin and etoposide. RAM+wPTX, weekly paclitaxel with ramucirumab. NSE: neuron specific enolase, CBDCA: carboplatin, RAM: ramucirumab, wPTX: weekly paclitaxel

(Fig. 6a, b), and even after 16 months, as evaluated with ^{18}F fluoro-2-deoxyglucose positron emission tomography (Fig. 6c, d). The elevated NSE levels decreased slightly after chemotherapy with carboplatin and etoposide, normalized after palliative surgery, and persisted at the normal value thereafter (Fig. 7).

The superficial esophageal and hypopharyngeal cancers had progressed before palliative gastrectomy was performed. However, esophagogastroduodenoscopy three months after the discontinuation of nivolumab revealed that the superfi-

cial esophageal cancer had disappeared, and the hypopharyngeal cancer had shrunk. Hypopharyngeal cancer was surgically resected, and a histological diagnosis of squamous cell carcinoma (pT1, pStage I) was made. The patient was doing well 28 months after preparation of this report.

Discussion

We herein report a case of advanced gastric NEC that was refractory to conventional chemotherapy but regressed in re-

sponse to nivolumab monotherapy (initiated for the treatment of residual tumors after palliative gastrectomy for severe bleeding). Sawayama et al. (9) reported a case of partial response of PD-L1 negative gastric NEC with liver and para-aortic lymph node metastases to nivolumab as the third-line regimen. Yan et al. (10) reported temporary regression of gastric NEC with nivolumab and chemotherapy, but the progression-free survival was ≥ 3.5 months. To our knowledge, ours is the first report of nivolumab monotherapy that achieved complete remission in gastric NEC; complete remission was maintained for at least 16 months after nivolumab was stopped, and the patient survival was confirmed to be 28 months as of the preparation of this report.

Although cases of complete remission have been reported in small- and large-cell neuroendocrine lung cancer (14-16), complete remission was reported in only 1 case among 157 gastrointestinal neuroendocrine cancers in a study evaluating the efficacy of platinum combination drug therapy (6). Thus, our case in which complete remission was achieved with nivolumab monotherapy suggests the promising efficacy of immunotherapy for gastric NEC. Our case is notable because complete remission was achieved even though the tumor cells were negative for microsatellite instability and had a low tumor mutation burden, so the efficacy of immunotherapy was hardly expected.

The synergistic effects of immune checkpoint inhibitors and other therapies, such as chemotherapy (17) and radiotherapy (18, 19), have been reported in non-small-cell lung cancer (17, 18) and melanoma (19). In our case, the target lesions of nivolumab therapy were the residual tumors present after palliative resection of the primary lesion. Whether or not resection of the primary lesion modulated the immune response against tumor cells and led to the efficacy of nivolumab is unclear. Further investigations are required to resolve this issue.

PD-L1 expression in tumor cells is an insufficient marker for selecting patients for immunotherapy (20). The efficacy of nivolumab has been reported in non-small-cell carcinoma, even in PD-L1-negative patients, and its efficacy regardless of PD-L1 expression has been reported in uterine cancer (21, 22). Although PD-L1 expression was not examined in the remnant lesions in our case, in which complete remission was achieved with nivolumab monotherapy, primary gastric NEC was negative for PD-L1. Thus, if sufficient presentation of tumor cell antigens is achieved, the efficacy of immune checkpoint inhibitors can be expected regardless of PD-L1 expression.

In conclusion, this case report describes the effectiveness of nivolumab for remnant lesions after palliative surgery for gastric NEC, including complete remission for at least 16 months and a survival for 28 months after discontinuation of nivolumab.

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

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