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A Case of Gastric Cancer with Neuroendocrine Carcinoma, Signet Ring Cell Carcinoma Components, and Intramural Metastases

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Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
Literature Search F
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Conflict of interest: None declared

Patient: Male, 67
Final Diagnosis: Gastric cancer with neuroendocrine carcinoma
Symptoms: —
Medication: —
Clinical Procedure: Total gastrectomy • splenectomy with D2 lymph node dissection
Specialty: Surgery

Objective: Rare co-existance of disease or pathology

Background: Many neuroendocrine carcinomas exhibit medullary infiltration and expanded proliferation. Differentiated tubular adenocarcinoma is frequently seen in the superficial region in many neuroendocrine carcinoma cases. However, the present case showed non-medullary infiltration and signet ring cell carcinoma in the superficial region, with intramural metastases distributed throughout the whole of the stomach.

Case Report: A 67-year-old man was referred to our institution for treatment of gastric cancer. Type IIc-like advanced gastric cancer was detected in the greater curvature of the middle body of the stomach. The patient underwent total gastrectomy, splenectomy with D2 lymph node dissection, and Roux-en-Y reconstruction with curative resection. The tumor was diagnosed as a large-cell endocrine carcinoma of the stomach. A solid growth of signet ring cells was seen in the mucosa and submucosa. Intramural metastases were observed in many other depressed lesions. Large-cell carcinoma invaded the submucosa, mainly in the intramural metastatic site. Metastasis to one lesser curvature lymph node was also seen on histological examination. The final diagnosis was a gastric cancer of type 0–IIc (T4a) [M] (with intramural metastases) at T4aN1H0P0M0 Stage IIIA. This patient has remained alive without recurrence for 72 months after surgery.

Conclusions: We recommend close preoperative examination of neuroendocrine carcinoma, taking intramural metastases into consideration.

MeSH Keywords: Carcinoma, Neuroendocrine • Carcinoma, Signet Ring Cell • Neoplasm Metastasis • Stomach Neoplasms

Full-text PDF: http://www.amjcaserep.com/abstract/index/idArt/896625

Background

The reported frequency of neuroendocrine carcinoma (NEC) of the stomach is relatively low; it accounts for 0.1% to 0.6% of all gastric carcinomas [1,2]. In NEC, there is a high frequency of capillary invasion, lymph node metastasis, and hematogenous metastasis, such as to the liver and lung, and the prognosis is poor. The macroscopic features of NEC include a localized-type tumor, such as types 1 or 2. Many NECs show medullary infiltration and expanded proliferation [3,4]. Well-to-moderately differentiated tubular adenocarcinoma is frequently seen in the superficial region in many NEC cases [5].

Here, a case of NEC that showed non-medullary infiltration and signet ring cell carcinoma in the superficial region with intramural metastases throughout the whole of the stomach is presented.

Case Report

A 67-year-old man with a history of diabetes mellitus and hypertension visited a local hospital complaining of a heavy feeling in the stomach. An upper gastrointestinal endoscopic examination revealed multiple oval ulcers that were 1–2 cm in size. The pathological diagnosis based on a biopsy specimen obtained from the mucosa around the ulcers was non-cancerous tissue; the specimen showed no atypical epithelial cells or necrotic tissue. The patient was subsequently treated with a proton pump inhibitor. The patient underwent a second upper gastrointestinal endoscopic examination at 2 weeks after the commencement of proton pump inhibitor therapy. The condition of the ulcers was not improved; the pathological diagnosis, based on a biopsy specimen from the shallow ulcer located in the anterior wall of the angle of the stomach, was poorly differentiated adenocarcinoma with neuroendocrine differentiation. The patient was referred to the Gastroenterology Center at Kurume University Hospital for further examination.

Figure 1. X-ray findings for the stomach showing IIc-like advanced-type cancer with fold convergence in the greater curvature of the middle body of the stomach.

The patient's body mass index was 27.9. He had an appendectomy scar on the right lower abdomen. The liver, spleen, and tumor were not palpable on physical examination. On laboratory examination, the gastrin level was elevated to 350 pg/mL (≤200 pg/ml). The serum levels of carcinoembryonic antigen, carbohydrate antigen 19-9, cancer antigen 72-4, and neuron-specific γ-enolase were all within the reference ranges. An X-ray examination revealed multiple irregular round ulcerative lesions in the greater curvature and lesser curvature of the upper body, in the anterior wall of the fornix, and in the anterior wall of the angle of the stomach. The largest lesion was diagnosed as IIc-like advanced-type cancer, with fold convergence in the greater curvature of the middle body of the stomach (Figure 1). An upper gastrointestinal endoscopic examination showed an irregular ulceration with fold convergence that was about 30 mm in size in the greater curvature of the middle body (Figure 2A). There were multiple small ulcers in the anterior wall extending from the upper body to the lower body (Figure 2B), and in the posterior wall of the upper body of the stomach (Figure 2C). The pathological diagnosis, based on biopsy specimens from the largest ulcer with fold convergence in the greater curvature of the middle body, an ulcer in the posterior wall of the upper body, and an ulcer in the anterior wall of the angle, was poorly differentiated adenocarcinoma with signet ring cell carcinoma. Thus, the diagnosis was IIc-like advanced-type gastric cancer in the greater curvature of the middle body with multiple intramural metastases in the stomach. The primary tumor was not detected, but swelling of the lymph node was recognized at the lesser curvature of the stomach on abdominal computed tomography scans. The patient was admitted to the hospital and underwent total gastrectomy, splenectomy with D2 lymph node dissection, and Roux-en-Y reconstruction on July 30, 2009.

The primary tumor was palpable in the greater curvature of the middle body, and no exposed tumor was seen in the serosa. Macroscopic metastasis was found in the lymph node at the lesser curvature of the stomach, but not in the liver or peritoneum. On macroscopic examination of the resected specimen, a IIc-like advanced-type primary cancer that was 41×28 mm in size was seen in the greater curvature of the middle body, and multiple depressed lesions were seen in the lower-to-upper body (Figure 3). A low-power histological view showed that tumor cells had invaded whole layers of the stomach wall and showed infiltrative growth from the muscularis propria to the serosa (Figure 4A). The high-power view showed monotonous large tumor cells with abundant cytoplasm and large irregular nuclei that had prominent nucleoli; mitotic figures were also seen (32 per 10 high-power fields) (Figure 4B). The tumor showed positive immunohistochemical staining with

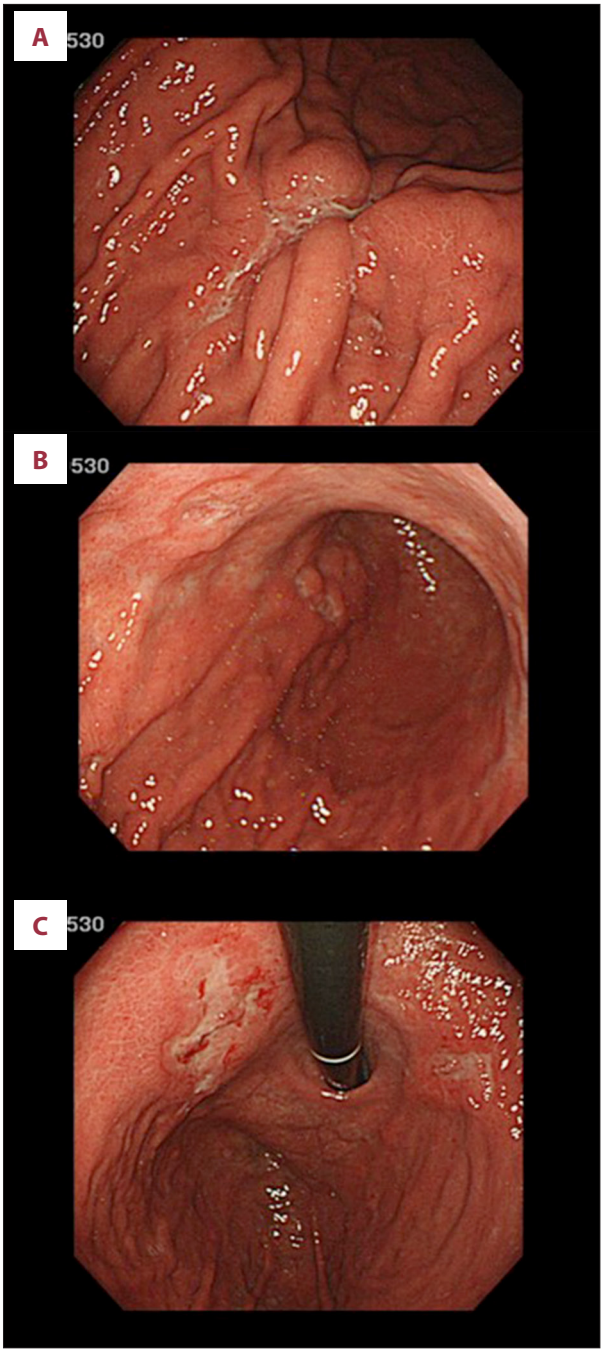

Figure 2. Images from endoscopic examination of the upper gastrointestinal showing: (**A**) an irregular ulceration with fold convergence approximately 30 mm in size in the greater curvature of the middle body; (**B**) multiple small ulcers in the anterior wall of the upper body extending to the lower body; and (**C**) multiple small ulcers in the posterior wall of the upper body of the stomach.

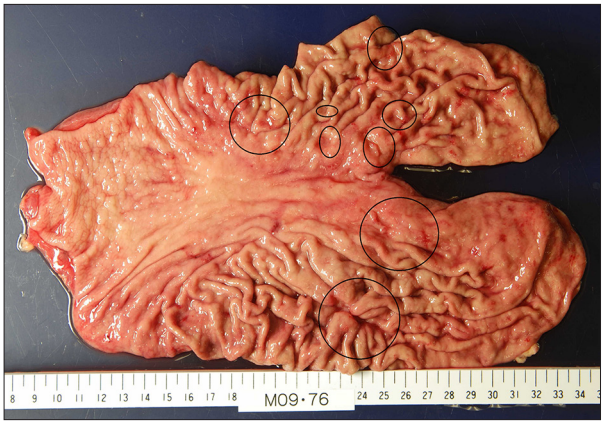

Figure 3. Macroscopic findings from the resected specimen indicating IIc-like advanced-type primary cancer, 41×28 mm in size, on the greater curvature of the middle body, and multiple depressed lesions extending from the lower to the upper body of the stomach (circles).

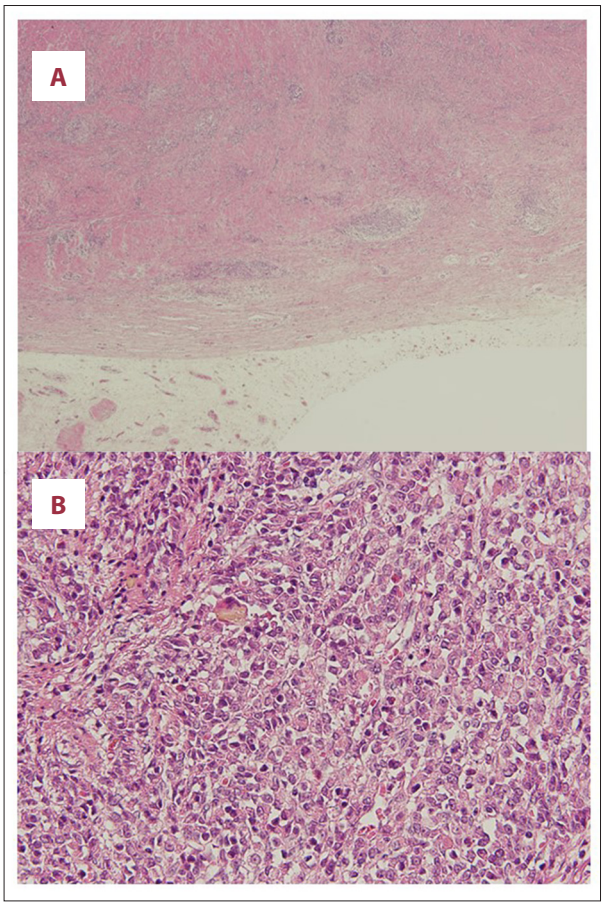

Figure 4. Photomicrographs of resected gastric tissue sections. (**A**) A low-power histological view. Tumor cells have invaded whole layers of the stomach wall and show infiltrative growth from the muscularis propria to the serosa (hematoxylin and eosin [H&E] ×40). (**B**) The high-power view shows monotonous large tumor cells with abundant cytoplasm and large irregular nuclei with prominent nucleoli; mitotic figures are also seen (32 per 10 high-power fields; H&E ×100).

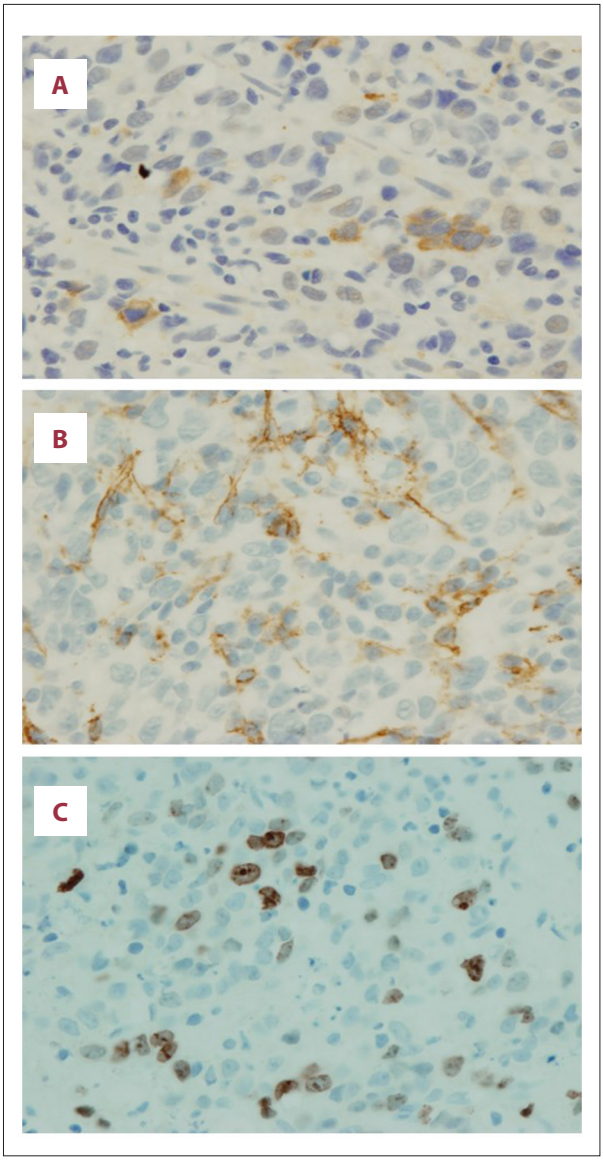

Figure 5. Immunohistochemical staining. Positive immunohistochemical staining with synaptophysin (**A**) (×400) and CD56 (**B**) (×400). (**C**) The Ki-67 index is 23.1% (×400).

synaptophysin and CD56 (Figure 5A, 5B). The Ki-67 index was 23.1% (Figure 5C). Thus, the histological diagnosis was large-cell endocrine carcinoma with moderate lymphatic and minimal venous invasion. Solid growth of signet ring cells was seen on the mucosa and submucosa (Figure 6).

Intramural metastases were observed in many other depressed lesions. Large-cell carcinoma invaded the submucosa, mainly at the intramural metastatic site (Figure 7). Consequently, this case was diagnosed as IIc-like advanced-type gastric cancer with intramural metastases extending throughout the whole stomach (Figure 8). Metastasis was seen in one lesser

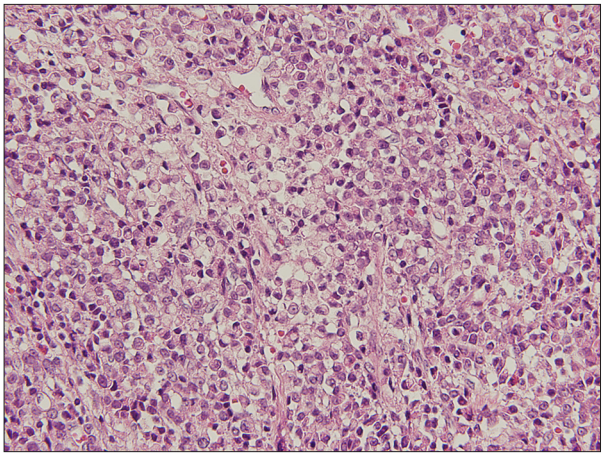

Figure 6. Photomicrographs of resected gastric tissue sections. Solid growth of signet ring cells can be seen in the mucosa and submucosa (H&E ×100).

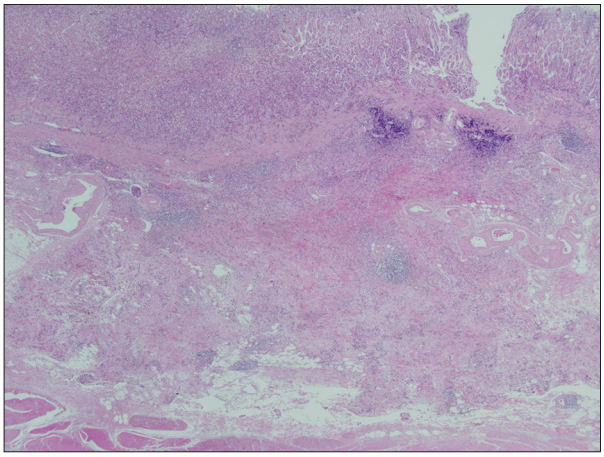

Figure 7. Photomicrographs of intramural metastatic site. Large-cell carcinoma invades the submucosa, mainly at the intramural metastatic site (H&E ×40).

curvature lymph node on histological examination. The final diagnosis was a gastric cancer of type 0-IIc (T4a) [M] (with intramural metastases) at T4aN1H0P0M0 Stage IIIA. The surgery decided upon was curative resection with a negative resection margin (R0). The patient's postoperative course was good, and he was discharged from the hospital on August 17, 2009. Subsequently, the patient was administered 300 mg of tegafur-uracil as postoperative adjuvant chemotherapy. He remains alive without recurrence at 72 months after surgery.

Discussion

The World Health Organization 2010 classification defined NEC as a subgroup of neuroendocrine neoplasms. Neuroendocrine neoplasms are classified as neuroendocrine tumors or NECs, according to their bioactivity, which is determined by the mitotic

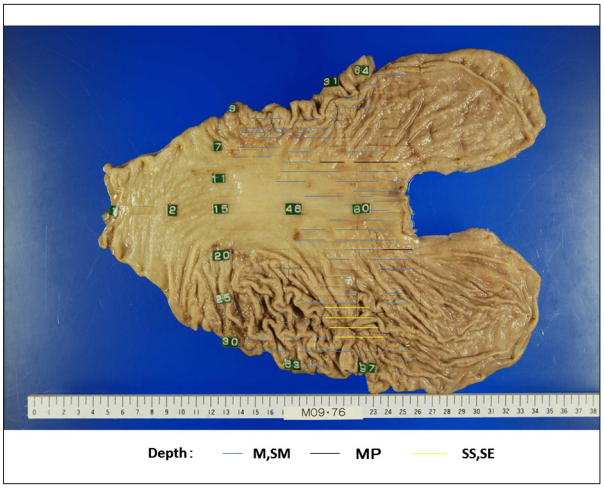

Figure 8. Depth and spread of cancerous lesions of the stomach. IIc-like advanced-type gastric cancer with serosal invasion at the greater curvature of the middle body of the stomach, and intramural metastases with mucosa or submucosal invasion involving the whole stomach are shown. M – mucosa; SM – submucosa; MP – muscularis propria; SS – subserosa; SE – exposed beyond the serosa.

rate (>20) and Ki67 index (>20%) [6]. NECs are positive for neuroendocrine markers such as chromogranin A, synaptophysin, and neural molecule (NCAM/CD56) on immunohistochemical staining [7]. The Japanese classification of gastric carcinoma defines NEC as a special type regarding the histological classification of gastric tumors, and considers NEC to be either of the small-cell type or of the large-cell type [8]. In our case, histological examination revealed monotonous large tumor cells with abundant cytoplasm and large irregular nuclei with prominent nucleoli; mitotic figures were also seen (32 per 10 high-power fields). The tumor exhibited positive immunohistochemical staining with synaptophysin and CD56. The Ki-67 index was 23.1%. Thus, the histological diagnosis was large-cell endocrine carcinoma.

Regarding the pathogenesis of NEC of the stomach, Iwafuchi et al. [5] reported four pathways: from common-type adenocarcinoma; from carcinoid tumor; from multi-potential stem cells; and from immature neuroendocrine cells. Recently, many NECs of the stomach have been considered to originate from common-type adenocarcinoma. The cell clone of the endocrine cell carcinoma is believed to originate from intramucosal adenocarcinoma. Differentiated tubular adenocarcinoma is thought to be particularly significant concerning the occurrence of endocrine cell carcinoma, because well-to-moderately differentiated tubular adenocarcinoma is frequently seen in the superficial regions in many NEC cases [9]. However, the proliferation of signet ring cells was seen in the superficial region in the present case. More than 50% of NECs are localized in the lower third of the stomach; approximately 80% of the macroscopic type of NECs are type 2, and many NECs show medullary infiltration and expanded proliferation [3,4]. However, the tumor in the current case was localized in the middle third of the stomach. The macroscopic type was IIc-like advanced type, and tumor cells had invaded whole layers of the stomach wall and exhibited infiltrative growth from the muscularis propria to the serosa. This patient underwent curative surgery, including total gastrectomy and splenectomy with D2 lymph node dissection, and was administered tegafur-uracil as postoperative adjuvant chemotherapy. Such multimodal therapy is considered to be effective in achieving long-term survival in patients with advanced neuroendocrine carcinoma of the stomach [10]. Iino et al. [11] reported that the biological characterization of NEC depended on the histological type of adenocarcinoma from which it was generated, or the component of adenocarcinoma that was dedifferentiated with the growth of the NEC tumor. In the present case, signet ring cells were seen and NEC cells showed infiltrative growth.

NEC exhibits high-level capillary invasion, aggressive growth, frequent lymph node metastases, hematogenous metastases, and a poor prognosis. The present patient had intramural metastases involving almost the whole stomach, but remains alive at the time of writing, without recurrence at 72 months after surgery.

Conclusions

Here, we reported a case of NEC that showed non-medullary infiltration and signet ring cell carcinoma in the superficial region with intramural metastases throughout the whole of the stomach. However, this patient is still alive at 72 months after surgery. The biological characterization of NEC is believed to depend on the histological type of adenocarcinoma responsible for generation of the NEC tumor. We recommend close preoperative examination of NEC, taking intramural metastases into consideration.

Acknowledgments

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Conflict of interest

The authors declare that they have no conflicts of interest.

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