Gastric adenocarcinoma is concurrent with metastatic neuroendocrine cancer treated with nivolumab and chemotherapy: A case report

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Abstract. Gastric adenocarcinoma concurrent with metastatic neuroendocrine cancer (NEC) is rare. In the present case report, a 39-year-old male was first pathologically diagnosed by gastric endoscopy as having a highly differentiated adenocarcinoma. Next, positron emission tomography-computed tomography examination and bone marrow biopsy confirmed extensive metastasis. Subsequently, the patient underwent 6 cycles of immunotherapy (nivolumab, 160 mg) and 5 cycles of chemotherapy based on the XELOX regimen (oxaliplatin + capecitabine). Following this, the patient received the final cycles of nivolumab and XELOX; however, the patient then succumbed. Further biopsy of the metastatic collarbone lymph nodes indicated NEC. Overall, the progression-free survival was ~3.5 months, and overall survival (OS) was ~6 months. The case presented the possibility of concurrent gastric adenocarcinoma and NEC in the clinic. In addition, the efficacy of a combined regimen such as immunotherapy and chemotherapy for such disorders still requires further validation in the future.

Introduction

Although gastric cancer is thought to be a highly heterogeneous disease (1), adenocarcinoma is still the most frequent pathological type in clinics. Neuroendocrine cancer (NEC) in the stomach is uncommon and only accounts for approximately 0.1-0.2% of all cancers that occur in the organ (2). Concurrent occurrence of gastric adenocarcinoma and neuroendocrine cancer is rare and has only been registered in a few case reports so far.

To date, such concurrent lesions have been classified into two subgroups according to their morphological features, named the composite-type and the collision-type; in the former, both elements seem to be mixed haphazardly, while in the latter, the tumors are considered double tumors with ‘a hand in hand’ conformation (3). Based on the complex relationship of the cancers, definite pathological diagnosis of such lesions is difficult. Most of the previous cases were diagnosed by gross specimens from surgery, such as gastrectomy. In 2010, the WHO named mixed adenoneuroendocrine carcinomas (MANECs), which present neuroendocrine cells (usually over 30% of all tumor cells) mixed with nonendocrine components (usually adenocarcinoma) (4), as a new category in the list of NECs. Interestingly, some of the previous cases are likely to be reclassified into this group retrospectively.

In this study, we present a case of gastric adenocarcinoma concurrent with metastatic NEC treated by nivolumab and chemotherapy (based on the XELOX regimen). The overall survival time of the patient was approximately 6 months. Our case addresses the possibility of concurrent gastric adenocarcinoma and NEC in the clinic; however, the efficacy of a combined regimen such as immunotherapy (nivolumab, for example) and chemotherapy for such disorders still needs further validation.

Case report

A 39-year-old man was first revealed by the 13C breath test to have an H. pylori infection during a routine physical examination; however, no treatment was adopted. Six months later, he suddenly presented tarry stool after drinking and underwent a gastric endoscopy, the pathological results of which indicated a well-differentiated adenocarcinoma on the gastric corpus (Fig. 1A); further immunohistochemical staining indicated the presence of CD4 (3+), CD8 (3+), MAGEA3 (2+), NY-ESO-1 (-), and PD-L1 (-) (Fig. 1B-F). Subsequent PET-CT examination showed the following: 1) Irregular wall thickening on the distal gastric corpus and antrum, particularly the greater curvature, indicated gastric cancer with adjacent fatty infiltration, and the greater omentum, ascending and transverse colon were likely to be involved; 2) Multiple lymph node metastases were present around the left supraclavicular and neck, to the right of the diaphragmatic feet, and in the left gastric artery area, celiac axis, liver and gastric ligament, small omental bursa, mesentery, retroperitoneal abdominal aorta and inferior vena cava; 3) The

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right and left femoral cavity, as well as multiple bones throughout
the body, presented metastatic lesions. The patient then under-
got a bone marrow biopsy, which confirmed metastatic cancer,
and FISH for Her-2 (negative). He then received the first cycle
of nivolumab (160 mg) treatment in another hospital and came
to our department. Further review of baseline images including
chest, abdomen and pelvis computed tomography (CT) scans
confirmed the previous imagological diagnosis (Fig. 2). Next, he

Figure 2. CT scan of the lesions previously reported by positron emission tomography-CT. (A) Abdominal enhanced CT indicates irregular wall thickening
on the distal gastric corpus and antrum with heterogeneous enhancement, accompanied by multiple lymph node metastasis (white arrows). (B) Pelvic CT with
bone window reveals extensive centrum and pelvic metastasis as well as marrow invasion (white arrows). CT, computed tomography.

Figure 1. Histological results of H&E staining and immunohistochemistry by gastric endoscopy. (A) Well-differentiated adenocarcinoma from the superficial
mucous membrane layer of the gastric corpus (H&E: magnification, x100). (B) CD4 membrane-positive cells clustered in the tumor (Magnification, x200).
(C) CD8 membrane-positive cells could also be seen in the tumor, but the area was smaller than that observed for CD4 (magnification, x200). (D) MAGEA3
staining was diffusely positive in nearly all tumor cells. (E) NY-ESO-1 and (F) PD-L1 staining was negative in all tumor cells (magnification, x200). H&E,
hematoxylin and eosin; CD, cluster of differentiation; MAGEA3, melanoma antigen family member A3; NY-ESO-1, New York esophageal squamous cell
carcinoma 1; PD-L1, programmed cell death 1 ligand 1.
received the second cycle of nivolumab and took capecitabine (1.5 g po twice per day, days 1-14 every 3 weeks) simultaneously. After that, another 3 cycles of nivolumab and XELOX (oxaliplatin 200 mg ivgtt, day 1+ capecitabine 1.5 g po twice per day, days 1-14) regimen treatments were executed; however, the intervals of the treatment plan were not executed as scheduled because of severe complications, including myelosuppression (grade 2-3 decreased platelet count and grade 1-2 anemia) and grade 1-3 hand-foot syndrome. Evaluation of the therapeutic effects was conducted by abdominal CT scan and a blood test for tumor markers as planned (Fig. 3). Stable disease (SD) and obvious progressive disease (PD) were detected after 3 and 5 cycles of treatment, respectively. He received the last 2 cycles of treatment even though the disease was considered to be PD. A further biopsy of the metastatic collarbone lymph nodes indicated neuroendocrine cancer with the following immunohistochemical staining: synaptophysin (+), CD56 (+), CK/CK7 (+), CK20 (−), Villin (−), Ki-67 (>75%) (Fig. 4). All the treatments were then ceased because of the poor performance status and severe complications; he died on December 12. Written informed consent was obtained from the patient’s father.

Discussion

Gastric adenocarcinoma concurrent with metastatic NEC is a rare phenomenon. To the best of our knowledge, concurrent gastric adenocarcinoma and NEC are uncommon and have only been registered in a few case reports (Table 1) (5-23). In our study, the patient was treated with nivolumab and chemotherapy. Although a transient disease regression was observed, the PFS (~3.5 months) and OS (~6 months) were still unsatisfactory; the efficacy of the combined regimen for such disorders needs further validation in the future.

In recent years, the detection of a neuroendocrine element in gastrointestinal cancers has been increasingly registered, which has often prevented concise diagnosis. In fact, the majority of previous cases (5,6,8-15,17-21,23) were diagnosed by gross specimens from surgeries such as gastrectomy because the neuroendocrine component is usually located in the mucosa, while the adenocarcinoma is seated in the deeper layers (7,14,21,24); furthermore, each of the two cancer types can occasionally present pathological evidence for the differentiation of the other (14,25-28) or the possibility of transformation from one type to the other (29). In our study, a MANEC (or, to be more precise, a high-grade MANEC by La Rosa’s report) (30) likely occurred according to the new categorization by WHO in 2010, considering that some reports have indicated that gastric NEC is prone to metastasis (13) and that the cells in metastatic sites are similar to those in the primary sites (2,11). However, due to the lack of gross samples and autopsy, it is impossible to estimate the percentage of cell elements in the tumor, and thus, a definite diagnosis was difficult.

To date, consensus guidelines for the management of double or multiple original cancers have not been established. La Rosa et al (30) suggested that priority should be given to the more malignant elements in the mass. For our case, some guidelines recommended management in the same manner as for gastric adenocarcinomas (31). For example, Li et al (17) reported that the FOLFOX regimen in such cases could achieve a 12-month disease-free survival. However, as NEC is notorious for its aggressive nature, most investigators have suggested that these elements should be considered therapeutic targets (32). In 1999, Mitry et al (33) first reported the efficacy of etoposide and cisplatin regimens in a cohort of 53 neuroendocrine cancers (including 3 cases that occurred in gastric cancer); Uchiyama et al (2) introduced S-1-based regimens as adjuvant therapy for 7 cases, and the 3-year overall survival rate was 83.8%. Okita et al (34) reported that cisplatin plus irinotecan regimens received a good response in 12 cases. Notably, Ip et al (35) reported a spontaneous complete regression of gastric NEC that seemed to be mediated by cytomegalovirus-induced cross-autoimmunity. In our case, the patient was treated with the XELOX regimen based on the first pathological results, and whether replacement with schemes such as etoposide and cisplatin could have led to tumor regression is unknown because of the poor physical states and severe complications of the patient at the terminal stage.

In recent years, immunotherapy has become increasingly popular in treating cancers, but the efficacy of such therapies is still being validated. A major problem for such therapies is the lack of reliable biomarkers for patient selection and response evaluation. Predictive biomarkers such as PD-L1 were under extensive study to this end; unfortunately, although expression of PD-L1 was detected in 50% of stage II and III gastric cancers (36), it has been found to be insufficient for patient selection for immunotherapy thus far (37). A phase I b clinical trial in 2016 first reported the application of pembrolizumab (another immunotherapy agent) for recurrent or metastatic gastric cancer (38). Subsequently, the efficacy of nivolumab in advanced gastric cancer was established in a phase 3 trial with a registered median overall survival of 5.26 months (39). Other agents targeting PD-L1 (such as avelumab) are still under clinical investigation. However, there are still no clinical trials concerning immunotherapeutic agents for concurrent or multiple cancers. In our case, the patient was treated with
Table I. Case reports of concurrent gastric adenocarcinoma and neuroendocrine cancer.

| Author, year | Gender | Age, years | Final pathological findings | Positive markers for NEC | Treatment | Overall survival time (Refs.) |
|--------------|--------|------------|----------------------------|--------------------------|-----------|-----------------------------|
| Okamoto et al, 2003 | Female | 78 | Poorly differentiated adenocarcinoma+NEC+hepatoid adenocarcinoma | CgA | Gastrectomy | 4 years and 6 months (5) |
| Yasuda et al, 2006 | Female | 74 | Poorly differentiated adenocarcinoma+NEC | CgA, NSE | Gastrectomy+chemotherapy (cisplatin+5-Fu) | 1 year and 10 months (6) |
| Park et al, 2007 | Male | 48 | Well differentiated adenocarcinoma+NEC | - | Gastrectomy+chemotherapy (cisplatin+etoposide, TS-1) | >5 years 3 months (7) |
| Kim et al, 2009 | Male | 77 | Poorly differentiated adenocarcinoma+NEC+hepatoid adenocarcinoma | CgA, Syn | Gastrectomy | 91 days (8) |
| Jung et al, 2009 | Male | 59 | Adenocarcinoma+large cell NEC | CD56 | Gastrectomy | Not reported (9) |
| Mróz et al, 2009 | Male | 56 | Poorly differentiated adenocarcinoma+NEC | CgA, Syn, Ki-67(70%) | Gastrectomy+adjuvant chemotherapy | Not reported (10) |
| Jang et al, 2010 | Male | 50 | Well differentiated+large cell NEC | CgA, Syn, NSE | Gastrectomy | Not reported (11) |
| Cho et al, 2010 | Male | 67 | Adenocarcinoma+large cell NEC | - | Gastrectomy | Not reported (12) |
| Terada et al, 2011 | Male | 76 | Adenocarcinoma+large cell NEC | CK, Syn, CgA, PDGF, Ki-67 (90%) | Gastrectomy+adjuvant chemotherapy (S-1) | Not reported (13) |
| Miguchi et al, 2012 | Male | 72 | Moderately differentiated adenocarcinoma+NEC | CgA, Syn, NSE, Ki-67 (95%) | Gastrectomy+adjuvant chemotherapy (S-1) | Not reported (14) |
| Nakayama et al, 2012 | Male | 74 | Poorly differentiated adenocarcinoma+NEC | Syn, CD56 | Endoscopic examination | ~2 years (15) |
| Lee et al, 2013 | Male | 70 | Well differentiated adenocarcinoma+NEC | CgA, Syn, CD56 | Endoscopic submucosal dissection | Not reported (16) |
| Li et al, 2014 | Male | 56 | Moderately differentiated adenocarcinoma+NEC | CgA, Syn, Vim, TTF-1, CD117, Ki67 (80%) | Gastrectomy+adjuvant chemotherapy (FOLFOX) | Not reported (17) |
| Lipi et al, 2014 | Male | 50 | Adenocarcinoma+NEC+hepatoid adenocarcinoma | AE1/AE3, CgA, Syn | Gastrectomy+adjuvant chemotherapy (cisplatin+etoposide) | Not reported (18) |
| Zhang et al, 2014 | Male | 68 | Adenocarcinoma+NEC+squamous cell carcinoma | CgA, Syn, Ki-67(70%) | Gastrectomy | Not reported (19) |
| Payet et al, 2015 | Male | 71 | Adenocarcinoma+large-cell NEC | Syn, AE1/AE3 | Gastrectomy | Not reported (20) |
| Aoyagi et al, 2016 | Male | 76 | Poorly differentiated adenocarcinoma+signet ring cell carcinoma+NEC | Syn, CD56, Ki-67(23.1%) | Gastrectomy+adjuvant chemotherapy (tegafur-uracil) | 72 months (21) |
| Mitchell et al, 2015 | Male | 70 | Moderately differentiated adenocarcinoma+NEC | AE1/AE3, NSE, Ki-67(<2%) | Gastrectomy | Not reported (22) |
| Mainali et al, 2017 | Male | 67 | Well differentiated adenocarcinoma+NEC | - | Gastrectomy | Not reported (23) |

CgA, Chromogranin A; NSE, neuron-specific enolase; Syn, synaptophysin; Vim, vimentin; TTF-1, thyroid transcription-1; NEC, neuroendocrine cancer.
the nivolumab plus XELOX regime; considering the reported PFS (5.8 months) and OS (11.8 months) of single XELOX in advanced gastric cancer (40), it is difficult to conclude whether such combined therapies could help prolong the OS for such patients; however, additional clinical studies are still needed in the future.

Concurrent gastric adenocarcinoma and NEC can occur in the clinic, and interpretation of the pathological results should be done cautiously in the absence of gross specimens. The efficacy of therapeutic strategies such as immunotherapy and chemotherapy still requires further validation.

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Availability of data and materials
All data generated or analyzed during this study are included in this published article.

Authors’ contributions
BY and MC performed the case study, collected the data and images of the case and produced the draft of the manuscript. JY, FL and HL critically analyzed the manuscript for important intellectual content. All authors read and approved the final manuscript.

Ethics approval and consent to participate
The present study was approved by the Medical Ethics Committee of the Hainan Branch of PLA General Hospital. Written informed consent was obtained from the patient's father.

Patient consent for publication
Written informed consent was obtained from the patient's father.

Competing interests
The authors declare that they have no competing interests.

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