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CASE REPORT

Mixed large and small cell neuroendocrine carcinoma of the stomach: A case report and review of literature

Ze-Feng Li, Hai-Zhen Lu, Ying-Tai Chen, Xiao-Feng Bai, Tong-Bo Wang, He Fei, Dong-Bing Zhao

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Abstract

BACKGROUND

Gastric neuroendocrine carcinoma (GNEC) is a rare histological subtype of gastric cancer, which is categorized into small cell and large cell neuroendocrine carcinomas. It is characterized by strong invasiveness and poor prognosis. Mixed large and small cell neuroendocrine carcinoma (L/SCNEC) is an extremely rare pathological type of gastric cancer, and there have been no reports on this situation until now.

CASE SUMMARY

Herein, we first present a 57-year-old patient diagnosed with L/SCNEC of the stomach. A 57-year-old Chinese male presented with epigastric discomfort. Outpatient gastroscopic biopsy was performed, and pathological examination revealed that the cardia was invaded by adenocarcinoma. The patient underwent laparoscopic-assisted radical proximal subtotal gastrectomy and was diagnosed with L/SCNEC. He refused adjuvant treatment and was followed up every 3 mo. Eight months after the operation, the patient showed no evidence of local recurrence or distant metastasis.

CONCLUSION

We advocate conducting further genomic studies to explore the origin of gastric large cell and small cell neuroendocrine carcinoma and using different chemotherapy schemes according to large or small cell neuroendocrine carcinoma of the stomach for clinical research to clarify the heterogeneity of GNEC and improve the prognosis of patients with GNEC.

Key Words: Gastric cancer; Neuroendocrine carcinoma; Subtypes; Tumorigenesis; Treatments; Case report

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Core Tip: To the best of our knowledge, there have been no previous reports on mixed large and small cell neuroendocrine carcinoma of the stomach. This case might contribute to improving our understanding of gastric neuroendocrine carcinoma. More basic and clinical researches are warranted to clarify the heterogeneity of gastric neuroendocrine carcinoma.

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INTRODUCTION

It has been reported that the incidence rate of gastric neuroendocrine carcinoma (GNEC) is relatively low and accounts for 0.1% to 0.6% of all gastric cancers[1]. However, the incidence rate has been increasing in the past 20 years[2]. Due to its high degree of malignancy and poor prognosis, GNEC is receiving increasing attention. In 2019, the World Health Organization (WHO) listed poorly differentiated GNEC separately from the type 4 gastric neuroendocrine tumor and further subdivided it into two subtypes: Gastric large cell neuroendocrine carcinoma and gastric small cell neuroendocrine carcinoma[3]. Herein, we first report a 57-year-old male diagnosed with mixed large and small cell neuroendocrine carcinoma (L/SCNEC) of the stomach.

CASE PRESENTATION

Chief complaints

A 57-year-old man was referred to our hospital for the treatment of gastric cancer.

History of present illness

Two months prior, he visited a clinic complaining of upper abdominal discomfort. Pathologic examination of the biopsy under esophagogastroduodenoscopy revealed cardiac adenocarcinoma in another hospital.

History of past illness

He had diabetes for 30 years, for which he was taking metformin daily.

Personal and family history

There was no relevant personal or family history.

Physical examination

Physical assessment revealed no abnormalities.

Laboratory examinations

Laboratory examinations, including the tumor marker levels, revealed no abnormalities.

Imaging examinations

Esophagogastroduodenoscopy showed that an ulcerative tumor was approximately 1-3 cm away from the esophagogastric junction with a deep ulcer bottom and covered with dirt and white moss on the surface (Figure 1). Contrast-enhanced computed tomography scans revealed uneven thickening of the lesser curvature of the cardia and corpus, in accordance with gastric cancer, and coalesced lymph nodes in the cardiac area, approximately 0.8 cm in diameter (Figure 2).

Postoperative pathological results

A gross examination of the surgically resected specimen showed that a protuberant tumor with a size of 3 cm × 1 cm × 0.6 cm could be seen at the esophagogastric junction. Microscopically, mixed large (70%)

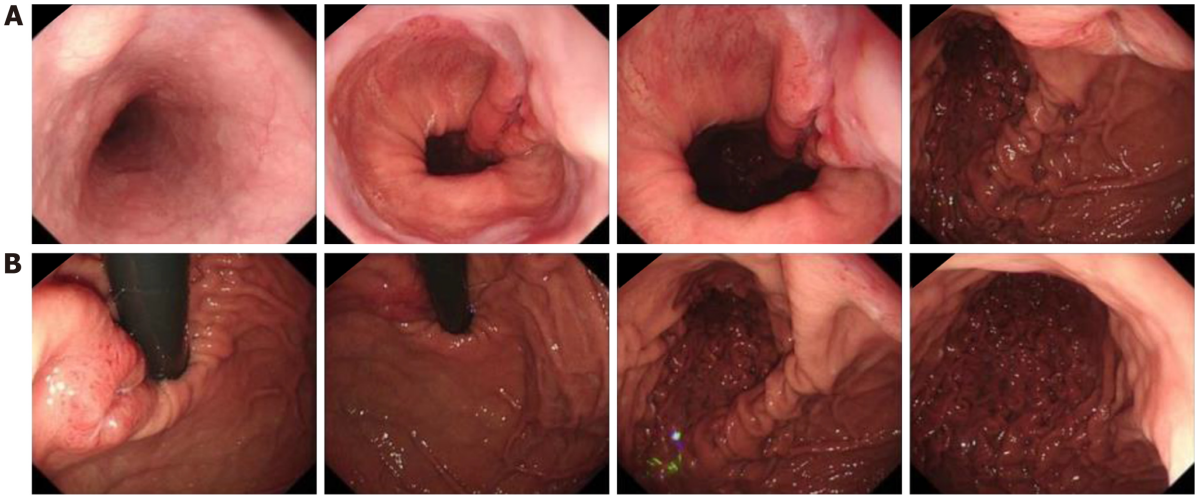

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Figure 1 Endoscopic images. A and B: An ulcerative tumor was approximately 1-3 cm away from the esophagogastric junction.

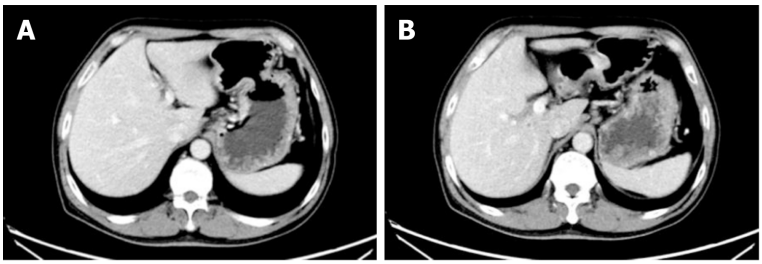

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Figure 2 Computed tomography images. A: Uneven thickening of the lesser curvature of the cardia and corpus, in accordance with gastric cancer; B: Coalesced lymph nodes in cardiac area, approximately 0.8 cm in diameter.

and small (30%) carcinoma cells invaded the propria muscularis layer, with a negative margin (Figure 3). Vascular tumor thrombus and nerve invasion could be seen. Some lymph nodes were found to have metastatic carcinoma (5/21). One of them was large cell carcinoma components. One of them was mixed large and small cell carcinoma components. Three lymph nodes were small cell carcinoma components (Figure 4). Immunohistochemistry (Figure 5) showed AE1/AE3 (2+), Syn (3+), CD56 (3+), CgA (2+), Ki-67 (60-70%), p53 (80%), AFP (-), c-Met (-), EGFR (-), GPC3 (-), HER2 (0), MLH1 (+), MSH2 (+), MSH6 (+), PMS2 (+), Sall4 (2+), and S-100 (-). In situ hybridization showed EBER (-). The pTNM classification was T2N2M0 (stage IIB).

FINAL DIAGNOSIS

The patient was diagnosed with gastric cancer (L/SCNEC) pT2N2M0 (stage IIB), accompanied by diabetes.

TREATMENT

We performed a laparoscopic-assisted subtotal gastrectomy with D2 lymphadenectomy. The patient refused adjuvant treatment.

OUTCOME AND FOLLOW-UP

The patient remained recurrence- and metastasis-free 8 mo after surgery.

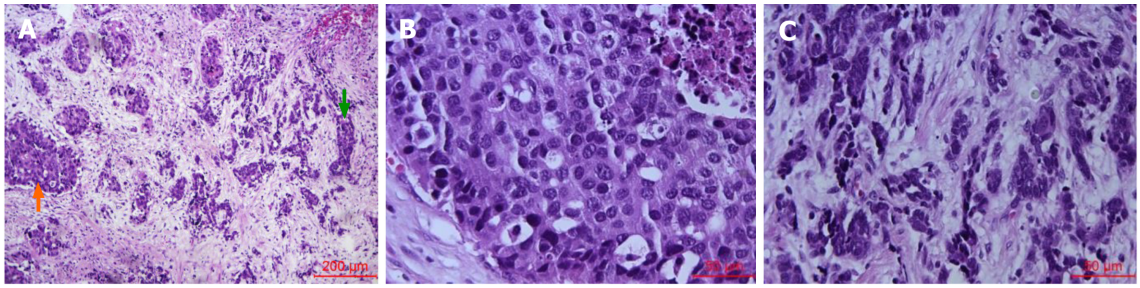

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Figure 3 Histological findings of the primary lesion. A: Mixed large and small cell neuroendocrine carcinoma of the stomach [hematoxylin-eosin (HE), × 100]. The pictures show large cell neuroendocrine carcinoma on the left side (orange arrow) and small cell neuroendocrine carcinoma on the right side (green arrow); B: The two components were separated clearly. Large cell neuroendocrine carcinoma (HE, × 400); C: Small cell neuroendocrine carcinoma (HE, × 400).

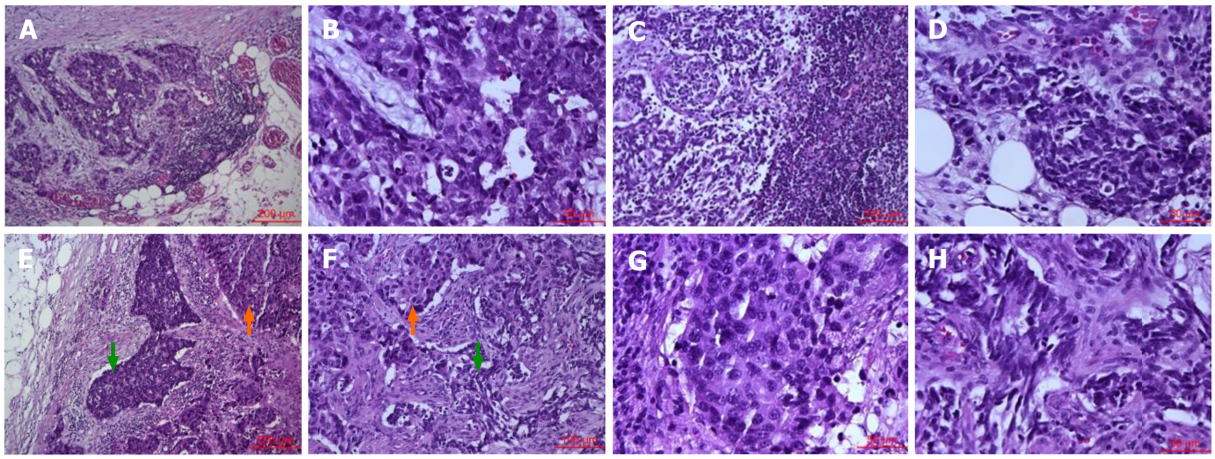

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Figure 4 Histological findings of metastatic lymph nodes. A and B: Metastatic lymph node with large cell neuroendocrine carcinoma [A, hematoxylin-eosin (HE), × 100; B, HE, × 400]; C and D: Metastatic lymph node with small cell neuroendocrine carcinoma (C, HE, × 200; D, HE, × 400); E and F: Metastatic lymph node with mixed large and small cell neuroendocrine carcinoma. The orange arrow points to large cell neuroendocrine carcinoma, and the green arrow points to small cell neuroendocrine carcinoma (E, HE, × 100; F, HE, × 200); G: Large cell neuroendocrine carcinoma components of mixed large and small cell neuroendocrine carcinoma lymph nodes (HE, × 400); H: Small cell neuroendocrine carcinoma components of mixed large and small cell neuroendocrine carcinoma lymph nodes (HE, × 400).

DISCUSSION

GNEC is a malignant tumor with poor biological behavior. The incidence rate of GNEC has been increasing in recent years[2]. In 2019, the WHO listed poorly differentiated GNEC separately from the type 4 gastric neuroendocrine tumor and further subdivided it into two types: large cell neuroendocrine carcinoma and small cell neuroendocrine carcinoma. Mixed adenoneuroendocrine carcinoma (MANEC) has also been expanded to mixed neuroendocrine non-neuroendocrine neoplasms (MiNEN), and it is stipulated that both neuroendocrine and non-neuroendocrine components should exceed 30%[3]. However, the cutoff point of 30% has been controversial for a long time[4]. Jiang *et al*[5] believed that more than 20% of neuroendocrine components could affect the prognosis in gastric adenocarcinoma, and Park *et al*[6] advocated that the cutoff value should be set at 10%. Even though the neuroendocrine component accounts for a relatively low proportion in the primary focus, it can become the main component in the metastatic lymph nodes, suggesting that the GNEC component has higher malignant behavior, and the vessels and lymphatic vessels could be invaded in the early stage[7]. This case of GNEC did not receive neoadjuvant therapy and was mixed with large cell and small cell neuroendocrine components, both of which were more than 30%. A few reports of L/SCNEC have been seen in the lung, uterus and other organs in the past[8,9]. However, to the best of our knowledge, this is the first time it has been reported in the digestive system.

The origin of GNEC and MiNEN has not been determined. One view is that during the proliferation of normal enterochromaffin-like cells, superimposed gene mutations result in gastric neuroendocrine tumor formation, which further progresses to GNEC, diffuse gastric adenocarcinoma and finally signet ring cell carcinoma[10-12]. Another view is that gastric neuroendocrine cells predominantly arise from neuroendocrine precursor cell clones occurring in preceding adenocarcinoma components, which

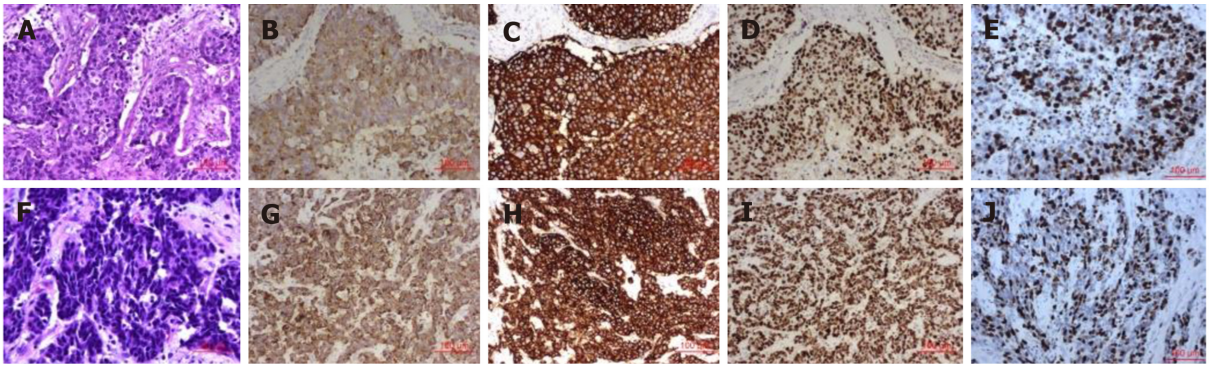

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Figure 5 Histological findings and immunohistochemical staining. A-E: Large cell neuroendocrine carcinoma [A, hematoxylin-eosin (HE), × 200] showed positive immunohistochemical staining for chromogranin A (B, × 200), synaptophysin (C, × 200) and P53 (D, × 200). The Ki-67 index was approximately 60% (E, × 200); F-J: Small cell neuroendocrine carcinoma (F, HE, × 400) showed positive immunohistochemical staining for chromogranin A (G, × 200), synaptophysin (H, × 200) and P53 (I, × 200). The Ki-67 index was approximately 60% (J, × 200).

transform into neuroendocrine cells during rapid clonal expansion. The adenocarcinoma component may become necrotic or desquamate, while the neuroendocrine component rapidly develops. Thus, MANEC seems to be a transitional stage in the transformation from gastric adenocarcinoma to GNEC. Gene sequencing[13-15] and mucin phenotype expression[16] of GNEC, gastric adenocarcinoma and two components in MANEC have tested and supported the hypothesis. GNEC is usually diagnosed at an advanced stage, which also supports this viewpoint. There is a potential consensus that adenocarcinoma cells and neuroendocrine cancer cells can originate from the same kind of precursor cells. However, Makuuchi *et al*[17] found that there were significant differences in gene expression between GNEC and gastric adenocarcinoma by whole exon sequencing. The vast majority of mutated genes in GNEC (517/557, 92.8%) were not mutated in gastric adenocarcinoma. Lewin[18] histologically divided MANEN into a combination type (two components adjacent but not mixed), collision type (two components cross mixed with each other) and double secretion type (tumor cells secreting mucus and expressing neuroendocrine markers at the same time). The tumorigenesis of different types may be distinct, which may explain the differences in the above research results.

For GNEC patients without distant metastasis, surgical resection of the lesion is still the first choice. At present, platinum-based chemotherapy is often used as the first-line treatment for patients with advanced GNEC who have lost the opportunity for radical operation. FOLFIRI (fluorouracil, leucovorin, and irinotecan) or FOLFOX (leucovorin, fluorouracil, and oxaliplatin) can be used as the second-line treatment. The effectiveness of molecular targeted therapy[19], immunotherapy[20] and peptide receptor radionuclide therapy in patients with GNEC needs to be further tested[21]. Okita *et al*[22] found that after receiving EP (cisplatin plus irinotecan) chemotherapy, the response rate of 12 GNEC patients with distant metastasis or postoperative recurrence was 75%. The median progression-free survival time was 212 d, and the median survival time was 679 d. Thus, the EP regimen showed good therapeutic effects. Ma *et al*[23] found that neoadjuvant therapy can improve the prognosis of patients with GNEC (the 5-year survival rates of the neoadjuvant therapy group and direct surgery group were 57.4% *vs* 28.5%, respectively). However, there was no effect between the two subgroups of neoadjuvant chemotherapy using regimens based on platinum agents or not. In addition, there has been much discussion about whether adjuvant chemotherapy after radical resection can improve the prognosis of patients with GNEC. In 2020, a multicenter study in China found that after propensity score matching, neither chemotherapy based on platinum agents nor chemotherapy based on 5-fluorouracil agents can improve the prognosis of these patients[24]. The heterogeneity of GNEC may be the reason for the difference in treatment response.

The prognosis of GNEC is worse than that of gastric adenocarcinoma[4], and the prognosis of MANEC is worse than that of gastric adenocarcinoma but better than that of GNEC[25]. A multicenter retrospective study included 503 patients with GNEC, 401 patients with MANEC and 2875 patients with gastric adenocarcinoma. After propensity score matching, the 5-year disease-free survival rates of GNEC and gastric adenocarcinoma were 47.6% *vs* 57.6%, respectively ($P < 0.001$); the 5-year disease-free survival rates of MANEC and gastric adenocarcinoma were 51.1% and 57.8%, respectively ($P = 0.02$) [26]. The high proportion of neuroendocrine components in MANEC often indicates poor prognosis[27, 28]. This may be related to the fact that the components of GNEC are more prone to distant metastasis and lack of responsive chemotherapy.

In our case, although small cell neuroendocrine carcinoma components accounted for a lower ratio in the primary focus, there were more lymph node metastases. Compared with large cell neuroendocrine carcinoma, small cell neuroendocrine carcinoma may have worse biological behavior, at least in this case. However, there are few studies comparing the incidence rate, biological behavior, treatment

modalities and prognosis of large cell GNEC and small cell GNEC. Xie *et al*[29] found that in 132 cases of GNEC, small cell carcinoma accounted for 23.7%, and the 3-year survival rate was 63.3%, while large cells accounted for 77.3%, and the 3-year survival rate was 41.6%. A retrospective clinical study also suggested that the prognosis of large cell GNEC was worse in Korea[30]. Whether the prognosis of L/SCNEC is different needs to be further explored in the future. In lung cancer with a higher incidence rate, next-generation sequencing studies have shown that large cell neuroendocrine carcinoma can be further subdivided into two mutually exclusive groups based on their mutational patterns: the small cell carcinoma-like type, characterized by TP53+RB1 co-mutation/loss and other small cell carcinoma-type alterations, including MYCL amplification; and the non-small cell carcinoma-like type, characterized by the lack of co-altered TP53+RB1 and nearly universal occurrence of non-small cell carcinoma-type mutations (STK11, KRAS, and KEAP1)[31]. The prognosis of lung large cell neuroendocrine carcinoma may be further improved by selecting the corresponding chemotherapy regimen according to different molecular subtypes[32].

At present, many scientists believe that some precursor cells in well-differentiated adenocarcinoma can differentiate into neuroendocrine cancer cells[33]. The tumor as a whole gradually becomes MANEC. Then, as adenocarcinoma cells undergo necrosis, they gradually progress to pure GNEC. In view of the two molecular subtypes of lung large cell neuroendocrine carcinoma, we believe that gastric large cell neuroendocrine carcinoma may also have two subtypes: "small cell carcinoma-like" and "adenocarcinoma-like". However, there are few gene sequencing studies in GNEC. The above hypothesis needs to be further verified by histology and genomics.

CONCLUSION

This report is the first case report on L/SCNEC of the stomach. There is no corresponding classification in the WHO 2019 classification of digestive system neuroendocrine neoplasms. Clinically, most of patients with GNEC did not receive different chemotherapy schemes according to large cells or small cells, which may cause confusion in clinical treatment. We report the first case of L/SCNEC of the stomach and advocate using different chemotherapy regimens according to large or small cell neuroendocrine carcinoma of the stomach for clinical research to clarify the heterogeneity of GNEC and improve the prognosis of patients with GNEC.

FOOTNOTES

Author contributions: Li ZF and Lu HZ contributed equally to this work; Zhao DB contributed to the conception and design of the study; Li ZF collected the data and wrote the initial draft of the manuscript; Lu HZ reviewed the pathological sections and analyzed and interpreted the data; Chen YT and Bai XF contributed to drafting and revising the manuscript; Wang TB and Fei H participated in the clinical management and follow-up of the patient; all authors made substantial contributions to the intellectual content of this paper and approved the submitted version.

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