Long-term survival of Gastric Mixed Neuroendocrine-non-neuroendocrine neoplasms (MiNENs): two case reports

front-line chemotherapy for gastric MiNENs

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Abstract

BACKGROUND

Gastric Mixed neuroendocrine-non-neuroendocrine neoplasms (MiNENs), mixed neoplasms consisting of neuroendocrine and non-neuroendocrine components are quite rare. Until now, most data on gastric MiNENs come from clinical cases, without large-scale retrospective studies or controlled clinical trials. Consequently, no consensus regarding the origin, molecular characteristics, or appropriate treatment of MiNENs has been reached so far. We conducted chemotherapy of irinotecan plus cisplatin (IP regimen) and surgery to two patients with gastric MiNEN, which has never been used in treating this kind of tumor, leading to their long-term survival for more than 3 and 7 years, respectively.

CASE SUMMARY

Case 1: A 63-year-old male was admitted to the hospital because of frequent upper abdominal pain. He was diagnosed as gastric MiNEN with metastases in the regional lymph nodes and the left liver after the upper gastrointestinal endoscopy and CT-scan. He received 4 cycles of IP regimen, then the gastrectomy and partial left liver resection were performed, followed by additional 2 cycles of IP chemotherapy. The patient has survived for more than 3 years without any evidence of recurrence or metastases.

Case 2: A 54-year-old female patient was admitted to the hospital with recurrent epigastric pain for more than seven years. She was diagnosed as gastric MiNEN after upper gastrointestinal endoscopy, followed by a laparoscopic gastrectomy. She underwent a total of 6 cycles of IP regimens after the surgery. Two years after that, the CT reexamination revealed metastatic lesions in the lower lobe of right lung and video-assisted thoracoscopic surgery (VATS) was performed. Now she has survived for more than 7 years without any evidence of recurrence or metastases.

CONCLUSION
IP regimen, combined with curative-intent surgery if feasible, could be considered as the priority in the choice of front-line chemotherapy for gastric MiNEN.

**Key Words:** Gastric; Irinotecan plus cisplatin; Long-term survival; Mixed Neuroendocrine-non-neuroendocrine neoplasms; MiNEN

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**Core Tip:** Mixed neuroendocrine-non-neuroendocrine neoplasm (MiNEN) is a rare tumor, and highly aggressive with poor prognosis (median OS less than 12 mo) and no consensus regarding the appropriate treatment has been reached so far. We conducted chemotherapy of irinotecan plus cisplatin regimen and surgery to two patients with gastric MiNEN, which has not been used to treat this kind of tumor before, leading to their long-term survival for more than 3 and 7 years, respectively. Our reports may provide a reference for other clinicians.

**INTRODUCTION**

Gastric MiNENs, mixed neoplasms consisting of neuroendocrine and non-neuroendocrine components are quite rare, accounting for about 7% of all gastric neuroendocrine neoplasms and 25% of all gastric poor differentiated neuroendocrine carcinomas, but their prevalence has not been explored specifically so far. Gastrointestinal tumor with an exocrine and a neuroendocrine component were first described by Cordier in 1924. Many different names had been used since then, causing confusion among clinicians, surgeons and pathologists, such as composite carcinoid, mucin-producing carcinoid argentaffin cell adenocarcinoma, mixed exocrine-endocrine tumors, mixed adenoneuroendocrine carcinomas (MANECs), and so on. In the 2019 WHO Classification of Tumors of the Digestive System, the term MiNEN has been used
when referring to this kind of tumor. Until now, most data on gastric MiNENs come from clinical cases, without large-scale retrospective studies or controlled clinical trials. Consequently, no consensus regarding the origin, molecular characteristics, or appropriate treatment of MiNENs has been reached so far.

As lacking the knowledge of gastric MiNEN, the prognosis is quite poor, presenting with short median survival of less than 12 mo. The preferred treatment for high-grade MiNENs is currently suggested to be combining etoposide and a platinum salt (EP regimen) or the combinations of 5-fluorouracil and irinotecan or temozolomide or amrubcin. However, we conducted chemotherapy of irinotecan plus cisplatin (IP regimen) and surgery to two patients with gastric MiNEN, leading to their long-term survival for more than 3 and 7 years, respectively. Here, we present the process of diagnosis and treatment and a brief review of the literature to improve our understanding of the tumor.

CASE PRESENTATION

Chief complaints
Case 1: frequent upper abdominal pain for over 1 mo
Case 2: recurrent epigastric pain for more than 7 years

History of present illness
Case 1: The patient felt frequent upper abdominal pain for over 1 mo so he took the upper gastrointestinal endoscopy and magnetic resonance imaging in local hospital. Then he was diagnosed as gastric MiNEN with metastases in the regional lymph nodes and the left liver. He came to our hospital soon after, and was accepted because of "gastric cancer".
Case 2: The patient had recurrent epigastric pain since 7 years ago, and the pain got worse on a empty stomach. She took omeprazole herself without obvious relief. Then she took upper gastrointestinal endoscopy in local hospital and was diagnosed as
gastric cancer. So the patient came to our hospital for surgery and was accepted because of "gastric cancer".

**History of past illness**

Case 1: hypertension for more than 10 years; hemiorrhaphy surgery 5 years ago. No other special information to mention.
Case 2: chronic nasosinusitis; thyroiditis; cholecystolithiasis; hepatic cyst; hepatic haemangioma. No other special information to mention.

**Personal and family history**

Case 1: the patient's father was dead, and his mother was healthy.
Case 2: the patient's father was dead; her mother and little brother was alive.

**Physical examination**

Case 1: T 36.5°C, P 86/min, R 14/min, BP 122/82mmHg. No enlarged superficial lymph nodes. No abdominal wall varicosis. No gastrointestinal type or peristalses. No other positive signs.
Case 2: T 37.1°C, P 80/min, R 16/min, BP 118/76mmHg. No obvious positive signs.

**Laboratory examinations**

Case 1: RBC 4.2×10¹²/L, Hb 110g/L, WBC 6.8×10⁹/L, PLT 126×10⁹/L
Case 2: RBC 3.8×10¹²/L, Hb 102g/L, WBC 8.4×10⁹/L, PLT 208×10⁹/L

**Imaging examinations**

Case 1: CT-scan revealed the tumor infiltration into the omentum majus, with metastases to regional lymph nodes and the left liver.
Case 2: CT showed the tumor infiltrated into the stomach wall and metastasizes to regional lymph nodes.
FINAL DIAGNOSIS
Case 1: gastric MiNEN (metastases to left liver)
Case 2: gastric MiNEN

TREATMENT
Case 1: the patient received 4 cycles of IP regimen as first-line chemotherapy, then the gastrectomy and partial left liver resection were performed followed by 2 cycles of IP chemotherapy.
Case 2: the patient underwent a laparoscopic gastrectomy, then underwent a total of 6 cycles of IP regimens. The video-assisted thoracoscopic surgery (VATS) to the metastatic lesions in the lower lobe of right lung was performed two years after that.

OUTCOME AND FOLLOW-UP
Case 1: the patient has survived for more than 3 years without any evidence of recurrence or metastases.
Case 2: After the VATS, the patient does not undergo any further chemotherapy or radiotherapy and has survived for more than 7 years without any evidence of recurrence or metastases.

DISCUSSION
MiNEN is rare, especially in the stomach. To date, there is no consensus on the definition of MiNEN, especially the minimum proportion of each components. According to WHO classification of digestive system tumors, MiNEN should contain both adenocarcinoma and neuroendocrine carcinoma components and each component is not less than 30%. However, this cutoff value has not been universally accepted, as it is defined arbitrarily rather than on proven clinical evidence and a minor (i.e., <30%) poorly differentiated neuroendocrine carcinoma (PDNEC) component can impair prognosis [1,9,10]. Pham et al [5] once reported a case in which the adenocarcinoma component accounted for 10-20% of the tumor, just as the case in our two patients. Park
et al. [11] found that a minor proportion (10-30%) of PDNEC component would negatively influenced the prognosis of patients with gastric MiNENs in a study including 88 patients. Consequently, the current 30% threshold, without sufficient prognostic value, may be not mandatory for defining MiNEN.

Most gastrointestinal MiNENs are highly aggressive, with poor prognosis and median survival of less than 12 mo [5,9]. At present, the diagnosis mainly relies on pathological examination and IHC of surgical specimen [5,10]. CK, carcinoembryonic antigen (CEA), and caudal type homeobox 2 (CDX2) are used as markers for adenocarcinoma components, and Syn, CgA, and CD56 for neuroendocrine components [12]. In our two cases, the adenocarcinoma components were positive for CK18 or CKpan, and neuroendocrine component positive for CgA and Syn.

Until now, most studies suggest that surgical resection should be the main treatment for gastrointestinal MiNENs. Pham et al. [5,12-14] argue that palliative surgery remains essential even if the patients have undergone distant metastases. Our two patients underwent resection of primary lesion and metastatic lesion, respectively and both of them achieved long-term survival, being in good condition, without any evidence of recurrence to date. Therefore, we believe that curative-intent surgery if feasible, turns to be crucial to the treatment of MiNEN, as recommended by other authors.

There are still no consensus regarding the standard front-line chemotherapy against MiNENs [5]. Platinum combined with etoposide (EP) regimen is found to be the most recommended first-line therapy for gastroenteropancreatic neuroendocrine carcinomas (GEPNECs) [5,15,16]. The preferred treatment for high-grade MiNENs is also suggested to be EP regimen or the combinations of 5-fluorouracil and irinotecan or temozolomide or amrubicin [1]. Yamaguchi et al. [17] compared IP regimen and EP regimen in treating GEPNECs, discovering that IP group had a higher response rate (50% vs. 28%, respectively; P= 0.001). When it comes to irinotecan and etoposide, there were some studies demonstrating a lower incidence of grade 4 adverse events and treatment-related deaths in irinotecan group than in etoposide group when treating digestive
neuroendocrine carcinoma \cite{15,17}. IP regimen is also better than irinotecan single agent when comparing progression-free survival (PFS) and disease control rate (DCR) \cite{18}. Therefore, we thought that IP regimen could be used for our two patients. Surprisingly, both of them achieved long-time survival for more than 3 years and 7 years, respectively, which are much longer than those in other studies \cite{5}. It may suggest that IP regimen could be considered as the priority in the choice of front-line chemotherapy for gastric MiNEN. To the best of our knowledge, we were the first to use IP regimen along with surgical resection for patients with gastric MiNENs.

To date, the effect of Ki67 proliferation index variation on prognosis remains unclear. Shi et al \cite{19} discovered that the Ki67 index would rise in 40% ($n = 30$) patients and decline in 13.3% patients with gastroenteropancreatic NEC during the treatment. In addition, Panzuto, Botling, and their colleagues \cite{20,21} found that the Ki67 index of patients tends to rise at time of disease progression, and median OS was significantly shorter in patients with rising Ki67 index (50.2 vs. 115.1, HR 3.89, 95%CI 1.91-7.94, $P < 0.001$). The Ki67 index of the patient in case 2 declined from 60% to 30% after IP regimen treatment, and led to a long-term survival. This, to some extent, may indicate that the decrease of Ki67 index is related to a better prognosis, which still needs further study.

At present, the most common genetic changes found in MiNENs include TP53, KRAS, BRAF, APC, PIK3CA and MYC, et al \cite{22-25}. We wonder if our two patients share some common genetic changes, which could be part of the reason for their long-term survival. Next-generation sequencing (NGS) tests were performed on the surgical specimens of them, revealing that they are all proved to be microsatellite stable (MSS), and the tumor mutation burden (TMB) was 4.06 mut/Mb and 2.03 mut/Mb, respectively. TP53 mutation was found in patient 1, and BRCA2 mutation, along with copy number increase in 9 genes (MET, FGFR1, FGFR4, CDK4, CDK6, CDKN2A, ERBB3, RIT1, and VEGFA) in patient 2. We may assume that MSS and TMB fewer than 10 mut/Mb could be associated with improved response to IP regimen from the tests result. It still needs further studies to explore what genetic changes may indicate better prognosis in patients with MiNEN receiving IP regimen treatment.
Indeed, gastric MiNEN is a rare malignant tumor without specific clinical symptoms. Histopathological and immunohistochemical examinations are requisite for pathologists and physicians to make a diagnosis. Palliative surgery remains essential even when patients have undergone distant metastases. In the choice of front-line chemotherapy, we believe that IP regimen could be considered as the priority. More prospective researches are urgently needed to explore better treatment options for patients with gastric MiNEN.

CONCLUSION
Gastric MiNEN is a rare malignant tumor without specific clinical symptoms. Histopathological and immunohistochemical examinations are requisite for pathologists and physicians to make a diagnosis. Palliative surgery remains essential even when patients have undergone distant metastases. In the choice of front-line chemotherapy, we believe that IP regimen could be considered as the priority. More prospective researches are urgently needed to explore better treatment options for patients with gastric MiNEN.

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