Letter to the Editor

Tumor recurrence with disseminated liver metastases in a patient with resected early gastric cancer: a case of mixed adenoneuroendocrine carcinoma (MANEC)

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Introduction

Mixed adenoneuroendocrine carcinoma (MANEC) is defined as a neoplasm containing both adenocarcinoma and neuroendocrine carcinoma (NEC) elements with each element comprising more than 30% of the tumor (1). The gastroenteropancreatic tract is the most common site of MANEC and approximately 20% of gastrointestinal MANECs found in stomach (1,2). This type of mixed exocrine-endocrine carcinoma is reported to be associated with deeper invasion, more malignant biological behavior, and poorer prognosis than pure gastric cancer (3). Here, we report a case of early-stage gastric MANEC that recurred as disseminated liver metastasis after curative resection. Although the tumor was found in early stage confined to submucosa and without lymph node metastasis, poorly differentiated carcinoma component, high Ki-67 index, and the presence of lymphovascular invasion (LVI) may be the factors related to aggressive tumor recurrence.

Case presentation

A 64-year-old male patient was admitted to our hospital for routine follow-up after resection of early gastric cancer (EGC). He underwent endoscopic submucosal dissection (ESD) and subsequent distal gastrectomy for MANEC about 20 months ago. He was asymptomatic and doing well, but carcinoembryonic antigen and carbohydrate antigen 19-9 were slightly elevated; 4.81 ng/mL and 44.71 U/mL, respectively. Computed tomography (CT) scan revealed disseminated liver metastases and slightly prominent perigastric omental infiltration near the gastroduodenostomy, which was not visible on the previous 6-month CT scan (*Figure 1A*,*1B*). Although he had a history of resected gastric cancer, it was a 1 cm T1b cancer with 1.95 mm submucosal invasion. Initially, ESD was performed, which revealed that the mass consisted of two distinct components: 30% consisted of malignant epithelial cells arranged in tubular formations, and 70% had a solid sheet configuration with extensive necrosis (*Figure 1C*). The tubular structures consisted of cuboidal to tall columnar cells characterized by nuclear enlargement and pleomorphism (*Figure 1D*). Conversely, the solid sheets consisted of tumor cells with small, round to oval nuclei and sparse cytoplasm with finely granular chromatin and inconspicuous nucleoli. Some components had polygonal cells with clear and abundant cytoplasm with numerous mitoses and extensive LVI (*Figure 1E*). Immunohistochemical (IHC) staining revealed that the solid component of the tumor was positive for synaptophysin

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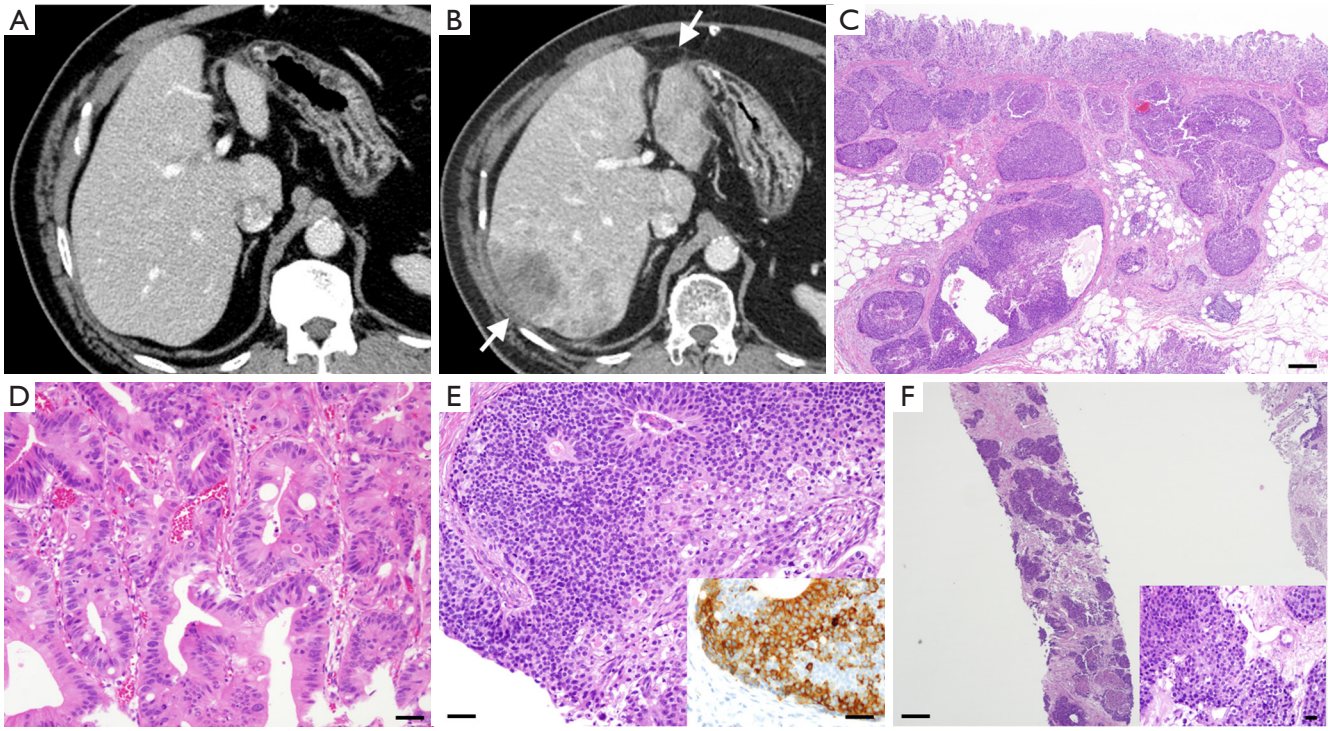

Figure 1 CT and histopathological findings. (A,B) Disseminated liver metastases were observed in both hepatic lobes (arrows), which were not visible on the previous 6-month CT. (C) Endoscopic submucosal resection of the stomach revealed a tumor comprises tubular formations in the mucosa and diffuse solid sheet and nest proliferation with extensive lymphovascular invasion (H&E, ×40; scale bar, 200 μm). (D) Tumor cells are tall and columnar in the tubular portion, with hyperchromatic nuclei and pleomorphism (H&E, ×200; scale bar, 50 μm). (E) Conversely, the tumor cells in the solid portion comprise small round cells with sparse cytoplasm, finely dispersed chromatin, and inconspicuous nucleoli. Some components have polygonal cells with clear and abundant cytoplasm. Numerous mitoses and necrosis are seen (H&E, ×200; scale bar, 50 μm). Immunohistochemical staining showed that the tumor was positive for synaptophysin (inset, ×200; scale bar, 50 μm). (F) Liver biopsies showed the same morphologic features as the gastric tumor cells, with a growth pattern of solid sheets and nests of small round cells (H&E, ×40; scale bar, 200 μm; inset, ×400; scale bar, 20 μm). CT, computed tomography; H&E, hematoxylin and eosin.

and CD56, with a high Ki-67 proliferation index (80%) (*Figure 1E*). These findings indicate MANEC, characterized by the association of tubular adenocarcinoma with poorly differentiated NEC. Subsequent gastrectomy was performed due to deep margin involvement, poorly differentiated cancer type, and diffuse LVI. Pathological analysis of the gastrectomy specimen showed no residual tumor or lymph node metastasis. Therefore, a percutaneous liver biopsy was performed to determine the origin of the liver metastasis. Liver biopsies revealed tumor cells similar to those observed in the ESD specimen with positivity for synaptophysin and CD56, and a high Ki-67 proliferation index of 80% on IHC staining (*Figure 1F*); therefore, recurrent tumor from gastric MANEC was diagnosed. He started chemotherapy with FOLFOX regimen. All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee(s) and with the Helsinki Declaration (as revised in 2013). Written informed consent was obtained from the patient for publication of this article and accompanying images. A copy of the written consent is available for review by the editorial office of this journal.

Discussion

MANEC refers to mixed adenocarcinoma and NEC, and is now included in the category of mixed neuroendocrine non-neuroendocrine neoplasm (MiNEN), which expands the spectrum of non-neuroendocrine lesions to include heterogeneous histologic variants other than

adenocarcinoma such as squamous cell carcinoma, sarcoma or others, according to the updated 2019 World Health Organization(WHO) classification (2,4). MiNEN are defined by the combination of at least two morphologically distinct components of neoplastic cells, including one neuroendocrine and one non-neuroendocrine component (5). They are rare, and account for less than 5% of all neuroendocrine neoplasms of the gastrointestinal tract (6). MiNEN can be classified into high, intermediate, and low grade, and our case is consistent with high-grade MiNEN, consisting of poorly differentiated NEC and non-neuroendocrine adenocarcinoma, in other words, MANEC (5). The two cell components can be difficult to distinguish from each other, especially when both are poorly differentiated, and their identification requires morphologic characterization and IHC techniques. CD56, chromogranin A and synaptophysin can be useful neuroendocrine markers. In our case, MANEC was initially diagnosed correctly after ESD showing distinct morphologic features with positive synaptophysin and CD56, but early detection of MANEC can often be missed because the NEC component is located in the deeper part of the mucosa or submucosa (7).

There are other morphologically and biologically mixed neoplasms which are described as adenocarcinomas with neuroendocrine differentiation (NED) or NECs with focal glandular differentiation, that do not respond to the 30% cut-off (8). In MANEC, the neuroendocrine and non-neuroendocrine components must be clearly separated from each other, and the neuroendocrine component should specifically represent positive neuroendocrine markers. With this distinction, other mixed tumor can be distinguished from MANEC such as carcinoma with interspersed neuroendocrine cells showing synaptophysin and chromogranin A positivity in isolated scattered cells, or amphicrine carcinoma; comprising tumor cells in the adenocarcinoma that simultaneously demonstrate the expression of NED, according to WHO 2022 classification of neuroendocrine tumors (2,9).

Surgical resection is the treatment of choice for MANEC although no therapeutic strategies have been established yet. Regarding chemotherapy, more aggressive tumor component should be the primary target of treatment (10). Genetic/molecular alterations in MANEC is poorly understood. According to previous meta-analysis of gastoenteropancreatic NECs, p53 expression was the most common mutation and microsatellite instability was found in about 10% of gastric and colorectal NECs (11,12). In MANECs, the molecular characteristics of NECs are largely similar to their adenocarcinoma tumor counterparts. It is necessary to carefully consider the pathologic features of each tumor component on a case-by-case basis for further treatment of MANEC.

Previous studies reported that NED components of gastric MANEC were more likely to metastasize to regional lymph nodes, and the predominance of NED was an independent risk factor for poor prognosis (13,14). Several studies demonstrated that NED ≥10% was a useful threshold indicating a worse prognosis compared with NED <10% (7,15,16). On the other hand, other studies reported that the degree of differentiation of tumor components and not the ratio of each component determines the clinical course and outcome of the disease (1,11). Any element with poor differentiation may be a cause of metastasis and has a major impact on the prognosis of the disease, and NEC element is usually the most aggressive element in MANEC (17).

Milione *et al.* reported that the Ki-67 index of the NEC component was the most crucial prognostic marker, as patients with Ki-67 ≥55% had an 8-fold risk of death and shorter median overall survival than those with Ki-67 <55% (18). Tomita *et al.* reported a case similar to ours that had LVI despite the intramucosal early gastric MANEC, and showed a high Ki-67 index (90%) comparable to ours (80%) (19). This case also showed early recurrence after curative ESD and rapid disease progression. Although our patient underwent curative surgical resection after ESD, postoperative tumor recurrence with aggressive progression occurred. Differentiated postoperative follow-up strategy should be considered such as shorter and meticulous follow-up care for this aggressive tumor patients.

In conclusion, we report a rare case of early gastric MANEC that was surgically resected but recurred as disseminated liver metastases in the postoperative follow-up period. For this unique and aggressive tumor, close surveillance with shorter follow-up period may be recommended, as well as early detection, and curative surgical resection.

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Footnote

Conflicts of Interest: Both authors have completed the ICMJE uniform disclosure form (available at https://qims.amegroups.com/article/view/10.21037/qims-23-1791/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee(s) and with the Helsinki Declaration (as revised in 2013). Written informed consent was obtained from the patient for publication of this article and accompanying images. A copy of the written consent is available for review by the editorial office of this journal.

References

1. Jeong BS, Hwang HW, Kim JW, Hwang IG, Park JY. Gastric Mixed Adenoneuroendocrine Carcinoma with Revised Diagnosis after Retrospective Pathologic Review. Korean J Helicobacter Up Gastrointest Res 2021;21:343-8.
2. Cattaneo L, Centonze G, Sabella G, Lagano V, Angerilli V, Pardo C, Bertani E, Spada F, Prinzi N, Pusceddu S, Fassan M, Fazio N, Milione M. Digestive MiNENs: Could histological classification and molecular characterization drive clinical outcome and therapeutic approach? Crit Rev Oncol Hematol 2023;188:104044.
3. Kim KH, Lee HJ, Lee SH, Hwang SH. Mixed adenoneuroendocrine carcinoma in the stomach: a case report with a literature review. Ann Surg Treat Res 2018;94:270-3.
4. Nagtegaal ID, Odze RD, Klimstra D, Paradis V, Rugge M, Schirmacher P, Washington KM, Carneiro F, Cree IA; WHO Classification of Tumours Editorial Board. The 2019 WHO classification of tumours of the digestive system. Histopathology 2020;76:182-8.
5. de Mestier L, Cros J. Digestive system mixed neuroendocrine-non-neuroendocrine neoplasms (MiNEN). Ann Endocrinol (Paris) 2019;80:172-3.
6. La Rosa S, Marando A, Sessa F, Capella C. Mixed Adenoneuroendocrine Carcinomas (MANECs) of the Gastrointestinal Tract: An Update. Cancers (Basel) 2012;4:11-30.
7. Yang G, Li D, Zheng F, Yang L. Long-term disease free survival of gastric mixed adenoneuroendocrine carcinoma treated with multimodality therapy: A case report. Mol Clin Oncol 2018;8:653-6.
8. de Mestier L, Cros J, Neuzillet C, Hentic O, Egal A, Muller N, Bouché O, Cadiot G, Ruszniewski P, Couvelard A, Hammel P. Digestive System Mixed Neuroendocrine-Non-Neuroendocrine Neoplasms. Neuroendocrinology 2017;105:412-25.
9. Rindi G, Mete O, Uccella S, Basturk O, La Rosa S, Brosens LAA, Ezzat S, de Herder WW, Klimstra DS, Papotti M, Asa SL. Overview of the 2022 WHO Classification of Neuroendocrine Neoplasms. Endocr Pathol 2022;33:115-54.
10. Düzköylü Y, Aras O, Bostancı EB, Keklik Temuçin T, Ulaş M. Mixed Adeno-Neuroendocrine Carcinoma; Case Series of Ten Patients with Review of the Literature. Balkan Med J 2018;35:263-7.
11. Frizziero M, Chakrabarty B, Nagy B, Lamarca A, Hubner RA, Valle JW, McNamara MG. Mixed Neuroendocrine Non-Neuroendocrine Neoplasms: A Systematic Review of a Controversial and Underestimated Diagnosis. J Clin Med 2020;9:273.
12. Girardi DM, Silva ACB, Rêgo JFM, Coudry RA, Riechelmann RP. Unraveling molecular pathways of poorly differentiated neuroendocrine carcinomas of the gastroenteropancreatic system: A systematic review. Cancer Treat Rev 2017;56:28-35.
13. Chen H, Shu M, Chen S, Xue L, Lin Y. Clinicopathological features and lymph node metastatic patterns of gastric mixed adenoneuroendocrine carcinoma. Histol Histopathol 2019;34:373-9.
14. Xie JW, Lu J, Wang JB, Lin JX, Chen QY, Cao LL, Lin M, Tu RH, Huang ZN, Lin JL, Zheng CH, Li P, Huang CM. Prognostic factors for survival after curative resection of gastric mixed adenoneuroendocrine carcinoma: a series of 80 patients. BMC Cancer 2018;18:1021.
15. Park JY, Ryu MH, Park YS, Park HJ, Ryoo BY, Kim MG,

Yook JH, Kim BS, Kang YK. Prognostic significance of neuroendocrine components in gastric carcinomas. Eur J Cancer 2014;50:2802-9.
16. Zou Y, Chen L, Wang X, Chen Y, Hu L, Zeng S, Wang P, Li G, Huang M, Wang L, He S, Li S, Jian L, Zhang S. Prognostic Threshold of Neuroendocrine Differentiation in Gastric Carcinoma: a Clinicopathological Study of 945 Cases. J Gastric Cancer 2019;19:121-31.
17. La Rosa S, Sessa F, Uccella S. Mixed Neuroendocrine-Nonneuroendocrine Neoplasms (MiNENs): Unifying the Concept of a Heterogeneous Group of Neoplasms. Endocr Pathol 2016;27:284-311.
18. Milione M, Maisonneuve P, Pellegrinelli A, Grillo F, Albarello L, Spaggiari P, et al. Ki67 proliferative index of the neuroendocrine component drives MANEC prognosis. Endocr Relat Cancer 2018;25:583-93.
19. Tomita Y, Seki H, Matsuzono E, Kobayashi Y, Sogabe S, Sugai N, Fujita J, Suzuki A. Early gastric mixed neuroendocrine-non-neuroendocrine neoplasm with early poor prognosis after endoscopic submucosal dissection: A case report. DEN Open 2022;2:e10.

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