

Clinicopathological features and lymph node metastatic patterns of gastric mixed adenoneuroendocrine carcinoma

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Summary. Aims. Mixed adenoneuroendocrine carcinoma (MANEC), also known as high- grade mixed neuroendocrine-non-neuroendocrine neoplasm (MiNEN) in the World Health Organization (WHO) classification of tumors of the endocrine organs (2017), is a rare gastric malignancy. Here, we present 10 cases of gastric MANEC and analyse their clinicopathological features and lymph node metastatic patterns.

Methods and results. Six patients were male, and four were female. The mean age of the patients was 67.9 years. Grossly, most tumors presented as ulcerative mass, located in gastric fundus or/and cardia. Microscopically, the neuroendocrine component, large cell neuroendocrine carcinoma in most cases (8/10), constituted 30-70% of the whole tumor. It was diffusely positive for CD56 or/and synaptophysin in all cases, but negative for chromogranin A in 9 cases. Ki-67 index was 50-80% in neuroendocrine component. The glandular component was moderately (6/10) or poorly (4/10) differentiated adenocarcinoma. Nine of 10 cases were positive for lymph node metastasis, with pure neuroendocrine component (6/9), or pure glandular component (1/9), or mixed components (2/9). The patients were treated with surgery, combining with chemotherapy (4/10), radiotherapy (2/10) and immunotherapy (1/10). Five patients died from tumor progress, with an average survival time of 18.6 months.

The dead cases had predominant neuroendocrine component in primary tumor or in metastatic lymph nodes.

Conclusions. Neuroendocrine component may determine the clinical behavior and outcome in gastric MANEC. Different metastatic component makes the selection of chemotherapy protocol more challenging.

Key words: Malignant mixed tumor, Neuroendocrine carcinoma, Gastric cancer, Metastasis

Introduction

Neuroendocrine tumors (NET) have become a research focus in gastrointestinal oncology in recent years. The major change in the World Health Organization (WHO) classification of tumors of the digestive system (2010) was pathological reclassification for NETs (Solcia et al., 2010). Mixed adenoneuroendocrine carcinoma (MANEC), renamed as mixed neuroendocrine-non-neuroendocrine neoplasm (MiNEN) in the new version of WHO classification of tumors (Kloppel et al., 2017), is a rare gastric malignancy, defined as a malignancy composed of epithelial and neuroendocrine components in the WHO classification of tumors, and at least 30% of either component should be identified to qualify for this definition (Solcia et al., 2010; Kloppel et al., 2017).

No systematic study has focused on metastasis of gastric MANEC. In the limited number of case reports and case series in the English language literature, lymph node metastasis was seen in most cases, although some

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did not describe the metastatic component in detail. It either contained a neuroendocrine component only, a glandular component only, or rarely a mix of neuroendocrine and glandular components (Yamazaki, 2003; Uchiyama et al., 2013; Gurzu et al., 2015; De Luca-Johnson and Zenali, 2016; Taguchi et al., 2016). Here, we present 10 case of gastric MANEC and their patterns of lymph node metastases. This is the first case series study describing in detail the lymph node metastatic pattern of gastric MANEC.

Materials and methods

Ten cases of gastric MANEC from 2012 to 2017 were retrospectively collected from Department of Pathology, the First Affiliated Hospital of Sun Yat-sen University. All tissues were fixed with 10% neutral buffered formalin and embedded in paraffin. Paraffin embedded specimens were sectioned at 4- μ m thickness and processed for hematoxylin and eosin staining and immunohistochemical analysis. All 10 cases were evaluated by two pathologists (Ling Xue and Yuan Lin) and classified as MANEC or high-grade MiNEN according to the criteria of WHO classification (2010, digestive system, and 2017, endocrine organs) (Kloppel et al., 2017; Solcia et al., 2010). Immunohistochemical staining was performed automatically on DAKO Autostainer, on formalin-fixed, paraffin-embedded tissue, with an EnVision kit (Dako, Carpinteria, CA, USA). The following FLEX ready-to-use primary antibodies from DAKO were used: CK7 (clone OV-TL12/30), monoclonal serum carcinoembryonic antigen (CEA, clone II-7), Ki-67 (clone MIB-1), CD56 (clone 123C3), synaptophysin (clone SY38) and chromogranin A (CgA, code IR502). Appropriate positive and negative controls were set on each slide.

Results

Clinical characteristics

The clinicopathological information of patients with

gastric MANEC is summarized in Table 1. Six patients were male, and four were female. The mean age of the patients was 67.9 years (range, 49-82 years; SD, 9.9 years; median age, 69 years). Tumors were mainly located in the upper stomach (gastric fundus or/and cardia) (9/10, including 1 case of gastric stump cancer), and only 1 case located in the antrum (case 10). Three of 10 invaded upward to the esophagogastric junction or lower esophagus (case 1, 3 and 9). Tumor sizes ranged from 1.5 \times 1 cm to 10 \times 8 cm. Stage III disease was found in 7 patients, stage I in 2 patients, and stage IV in 1 patient.

Upper abdominal pain was the most common symptom (6/10). Other common complaints included abdominal distension (4/10), dysphagia (4/10), weight loss (4/10), acid regurgitation and belching (3/10). Half of patients with tumors located in the upper stomach had significant dysphagia (4/8). None of the patients had hematochezia and melena. The patient with gastric stump cancer underwent subtotal gastrectomy 47 years ago because of duodenal ulcer (case 7). Two patients had type 2 diabetes, and 1 had hypertension. Three of 10 patients had a history of smoking. No family tumor history was declared.

Endoscope and abdominal computed tomography (CT) scan were performed in each patient. Ulcerative mass was the most commonly found by gastroscopy examination (7/10) (Fig. 1A). CT scan demonstrated wall thickening or mass formation protruding into the cavity (10/10), with regional lymphadenopathy (9/10) (Fig. 1B). However, neither gastroscopy examination nor CT scan could tell gastric MANEC from adenocarcinoma.

One patient (case 10) was mildly anaemic, with haemoglobin level of 112 g/L. CEA was elevated (5.23, 9.88, 8.29 and 16.68 μ g/L, respectively; reference range: 0-5 μ g/L) in 4 of 10 patients (case 1, 6, 8 and 9), and other serum tumor markers, including α -fetoprotein (reference range: 0-20 μ g/L), cancer antigen (CA)-125 (reference range: 0-35 U/mL), CA-19-9 (reference range: 0-35 U/mL) and squamous cell carcinoma antigen (reference range: 0.00-1.50 μ g/L), were within normal

Table 1. Clinical data of gastric mixed adenoneuroendocrine carcinomas.

No.	Age/sex	Site	Size(cm)	TNM	Adjuvant therapy	Follow-up
1	63 yr/F	Fundus, cardia	8.0 \times 8.0	T4N3M0	Chemotherapy (SOX, 1cycle)	Liver M 1mos; DOD 7mos
2	59 yr/M	Fundus, cardia	7.0 \times 6.0	T4bN2M1	Chemotherapy (EP, 6 cycles) +radiology	Liver M 12mos; DOD 26mos
3	49 yr/M	Upper stomach	4.0 \times 2.5	T4aN3bM0	Chemotherapy (EP, 8 cycles and FOLFIRI, 6 cycles) +radiology +immunotherapy	Recurrent 3mos; bone M 22mos; DOD 26mos
4	68 yr/M	Fundus	1.5 \times 1.0	T2N0M0	N/A	DOD 24mos
5	70 yr/M	Fundus	3.5 \times 2.2	T4aN3aM0	Chemotherapy (EP, 7 cycles)	Recurrent 22mos; AWT 26mos
6	62 yr/F	Fundus, cardia	5.0 \times 4.0	T4N1M0	N/A	Node M 6mos; AWD 24mos
7	82 yr/M	remnant stomach	3.0 \times 3.0	T4aN1M0	N/A	Liver M 5mos; DOD 10mos
8	78 yr/M	Fundus, cardia	8.0 \times 6.0	T4aN2M0	N/A	ANE 12mos
9	73 yr/F	Fundus, cardia	10.0 \times 8.0	T4N3M0	N/A	ANE 12mos
10	75 yr/F	Antral	2.5	T1N1M0	N/A	AFD 6mos

SOX, S1/oxaliplatin; EP, etoposide/platinum; FOLFIRI, fluorouracil, leucovorin, and irinotecan; M, metastasis; DOD, dead of disease; AWD, alive with disease; ANE, alive, not evaluated; AFD, alive, free of disease.

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limits in all patients.

Gross and histological findings

Preoperative biopsy was performed on each patient, and the pathological diagnosis was adenocarcinoma (7/10), poor-differentiated carcinoma (2/10, case 5 and case 10), or neuroendocrine carcinoma (NEC) (1/10, case 4), respectively.

The lesions presented as ulceration, gastric wall thickening and elevated mass. According to Borrmann

classification, 7 cases were classified as type III (Fig. 1C), 2 cases were type I (case 7 and case 10), and 1 case was type II (case 4).

All 10 cases were diagnosed as MANEC or high-grade MiNEN according to the criteria of WHO classification (2010, digestive system, and 2017, endocrine organs) (Solcia et al., 2010; Kloppel et al., 2017). The histological and immunohistochemical features are listed in Table 2. Microscopic examination revealed glandular and neuroendocrine components with distinct morphological features that were closely

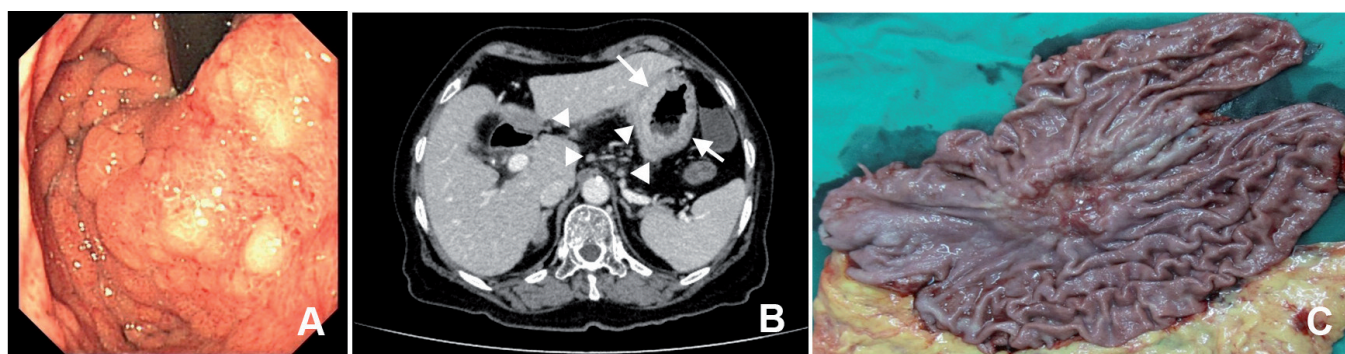


Fig. 1. Imaging and gross features of gastric MANEC. **A.** Most cases were found as ulcerative mass by gastroscopy. **B.** Contrast-enhanced CT showed wall thickening in gastric cardia and fundus (arrow), with metastases in the lymph nodes (arrow head). **C.** Gross examination showed a Borrmann III type tumor in gastric cardia and fundus.

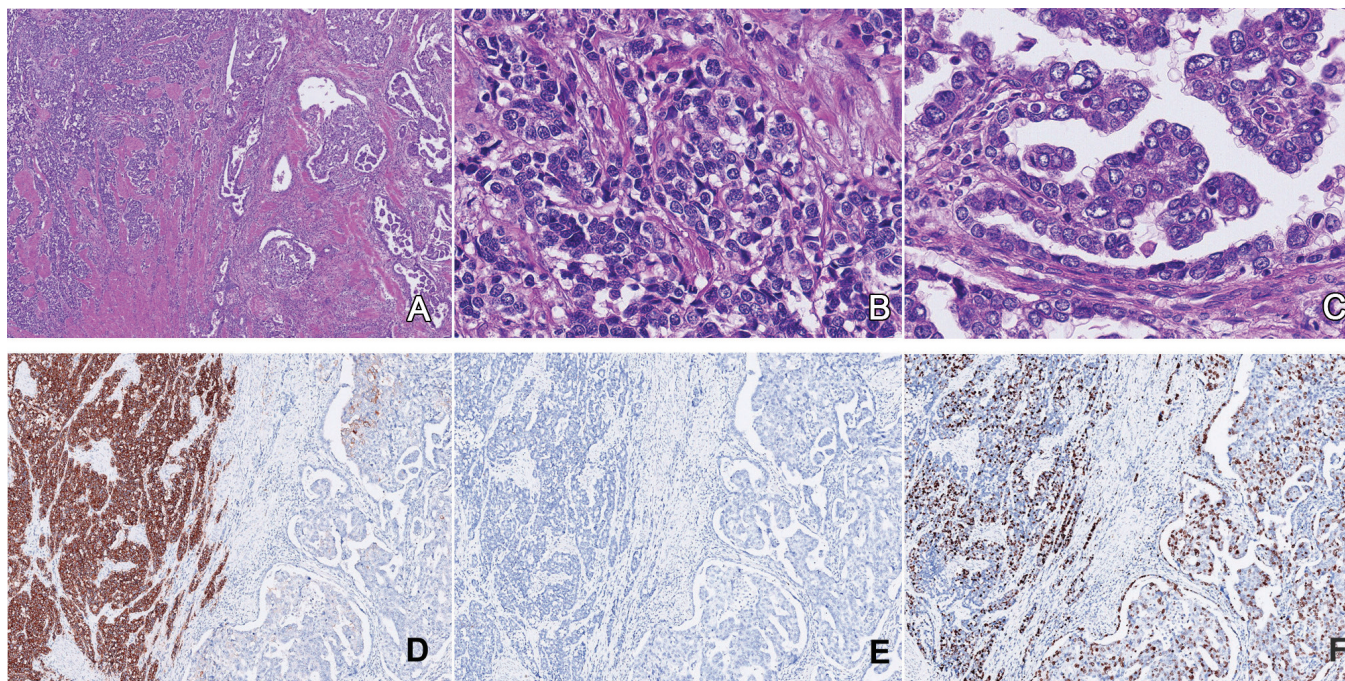


Fig. 2. Histological findings of gastric MANEC. The tumor was composed of neuroendocrine (**A left, B**) and glandular components (**A right, C**). Immunohistochemical staining showed positive immunoreactivity for synaptophysin (**D left**) in neuroendocrine component, but negative in glandular component (**D right**). Chromogranin A was negative in both components (**E**). Ki-67 staining showed high proliferation activity in both components (**F**). A, D-F, x 100; B, C, x 400.

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juxtaposed (8/10) (Fig. 2A) or intermingled (2/10). The neuroendocrine component constituted 30-70% of the whole tumor (Table 2). Six cases were composed of neuroendocrine component predominantly, 2 cases glandular component predominantly, and 2 cases equal components. The neuroendocrine component in 8 of 10 cases was large cell neuroendocrine carcinoma, composed of monomorphic large cells with prominent nucleoli, forming rosette-like or pseudoglandular structures (Fig. 2B). The mitotic figures ranged from 34 to 188 per 10 high-power fields (2 mm²). Two cases were small cell neuroendocrine carcinomas with 66 and 86 mitoses per 10 high-power fields respectively (case 3 and case 8). The glandular component was moderately (6/10) (Fig. 2C) or poorly (4/10) differentiated adenocarcinoma.

As to the neuroendocrine component, there was diffusely positive immunoreactivity for CD56 or/and synaptophysin in all cases (Fig. 2D), but negative for CgA in 9 of 10 cases (Fig. 2E). Ki-67 staining highlighted a proliferation index of 50-80% (Fig. 2F). CD56, synaptophysin and CgA, were negative in the glandular component in all cases (Fig. 2D,E). Only 1 case showed focal immunoreactivity for synaptophysin in glandular component (case 4). Scattered positive cells for CD56, synaptophysin or CgA did not qualify for neuroendocrine differentiation. Immunostaining for CK7 and monoclonal CEA was variously positive, and Ki-67 index ranged between 15% and 80% in glandular area (Fig. 2F).

The total number of dissected lymph nodes was 21 to 63 (Table 2). Nine of 10 cases were positive for lymph node metastasis, with the number of positive lymph nodes ranging from 1 to 20. The highest lymph node metastasis rate was 32% (case 3, 20/63). NEC was the predominant component in positive nodes, including pure NEC (36/61) or mixed with glandular (11/61). The metastatic component in 6 cases was pure neuroendocrine (Fig. 3A-C), 1 case was pure glandular

(Fig. 3D-F), and 2 cases had mixed components (case 3 and case 9) (Fig. 3G-I). The metastatic components in the lymph nodes resembled the gastric primary tumor morphologically, with positive immunoreactivity for CD56 or/and synaptophysin in the neuroendocrine component but negative immunoreactivity in the glandular component (Fig. 3C,F,I).

Treatment and outcome

All patients were clinically diagnosed with advanced gastric cancer and subsequently proceeded to gastrectomy and lymphadenectomy, 9 of whom with radical gastrectomy, and 1 with palliative gastrectomy (case 2). Postoperative chemotherapy was performed in 4 patients, including the protocols of EP (etoposide/platinum; 60-80 mg/m² Etoposide on day 1 to 5 and 20 mg/m² Cisplatin on day 1 to 4), SOX (S1/oxaliplatin; 130 mg/m² oxaliplatin on day 1, and 40-60 mg of S-1 twice daily for 2 weeks, followed by a 1-week rest) and FOFIRI (fluorouracil, leucovorin, and irinotecan; 180mg/m² irinotecan and 200mg/m² 1-leucovorin by intravenous infusion on day 1 and FU 400 mg/m² intravenous bolus on day 1, followed by 2,400 mg/m² continuous infusion administered over days 1 and 2). Two patients were subsequently treated combining with local radiotherapy, and 1 with immunotherapy. (Table 1)

All cases were followed up (Table 1), but 3 cases had no radiographic reexamination. Five patients died from tumor progress, and their stages were IIIc, IV, IIIc, Ib and IIIa respectively. The survival time ranged from 7 to 26 months, with an average of 18.6 months. As to the 5 survival cases, the follow-up time ranged from 6 to 26 months, with an average of 16 months, and their stages were IIIc, IIIa, IIIb, IIIc and Ib, respectively. Interestingly, all dead cases had predominant or at least half NEC component. However, in the survival cases, NEC component was predominant in 3 cases, and

Table 2. Histopathological features and lymph node metastasis patterns of gastric mixed adenoneuroendocrine carcinomas.

No.	Neuroendocrine component						Glandular component					Lymph node metastasis pattern		
	Percentage of Endo	component	Mitoses /10HPF	CD56	syn	CgA	Ki67	component	CD56	syn	CgA	Ki67	Positive node No.	Metastatic component
1	50%	LCNEC	110	+	+	-	70%	MD AC	-	-	-	40%	7/27	NEC (7/7)
2	70%	LCNEC	58	+	F+	-		PD AC	-	-	-		6/32	NEC (6/6)
3	50%	SCNEC	66	+	+	-	80%	PD AC	-	-	-	60%	20/63	AC+NEC(10/20),NEC(9/20),AC(1/20)
4	70%	LCNEC	81	+	+	-	60%	MD AC	-	F+	-	15%	0/21	/
5	70%	LCNEC	41	-	+	+	60%	MD AC	-	-	-	80%	10/47	NEC(10/10)
6	60%	LCNEC	188	+	+	-	70%	MD AC	-	-	-		1/42	NEC(1/1)
7	70%	LCNEC	34	+				MD AC	-				1/42	NEC(1/1)
8	30%	SCNEC	86	+	-	-	60%	PD AC	-	-	-	80%	4/40	AC(4/40)
9	30%	LCNEC	36	+	+	-	50%	PD AC	-	-	-	40%	11/61	AC (9/11), AC+NEC (1/11), NEC (1/11)
10	60%	LCNEC	139		+	-	80%	MD AC	-	-	-	60%	1/38	NEC(1/1)

Endo, neuroendocrine; syn, synaptophysin; CgA, chromogranin A; HPF, high power field; LCNEC, large cell neuroendocrine carcinoma; MD, moderately-differentiated; AC, adenocarcinoma; NEC, neuroendocrine carcinoma; F, focal; PD, poorly-differentiated; SCNEC, small cell neuroendocrine carcinoma.

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glandular component in the other 2 cases. Moreover, dead cases had higher lymph node metastatic rate (34/185 vs 27/228, 18.4% vs 11.8%), and most importantly, NEC component metastasizing to lymph nodes was more predominant in dead group than that in survival group (23/34 vs 13/27). Surprisingly, the average age of dead cases group was younger than the survival group (64.2 years vs 71.6 years), and there were more males in the dead cases group (4 males and 1 female, vs 2 males and 3 females).

Discussion

Gastric carcinoma with neuroendocrine differentiation is divided into the following categories: (1) carcinomas with scattered neuroendocrine cells; (2) composite glandular–neuroendocrine carcinomas; (3) collision tumors; (4) amphicrine tumors; and (5)

combination of the previous four (Bartley et al., 2011). According to this classification, the present case series, should be classified as a composite or collision tumor. About the derivation of the cellular components, the debate focuses on composite or collision. Recently, the composite hypothesis, in which the mixed components are derived from common epithelial stem cells with multidirectional differentiation, seems to be more widely accepted than the collision hypothesis, in which the components come from two separate cell types (multipotential epithelial stem cells and primitive neuroendocrine cells) located in proximity to one another incidentally (Fukui et al., 2001; Ishida et al., 2014). In the present case 3 and case 9, the primary and metastatic tumors contained both glandular and neuroendocrine components, which supports the composite hypothesis. First, the metastatic tumor cells preserve the potential of multidirectional differentiation,

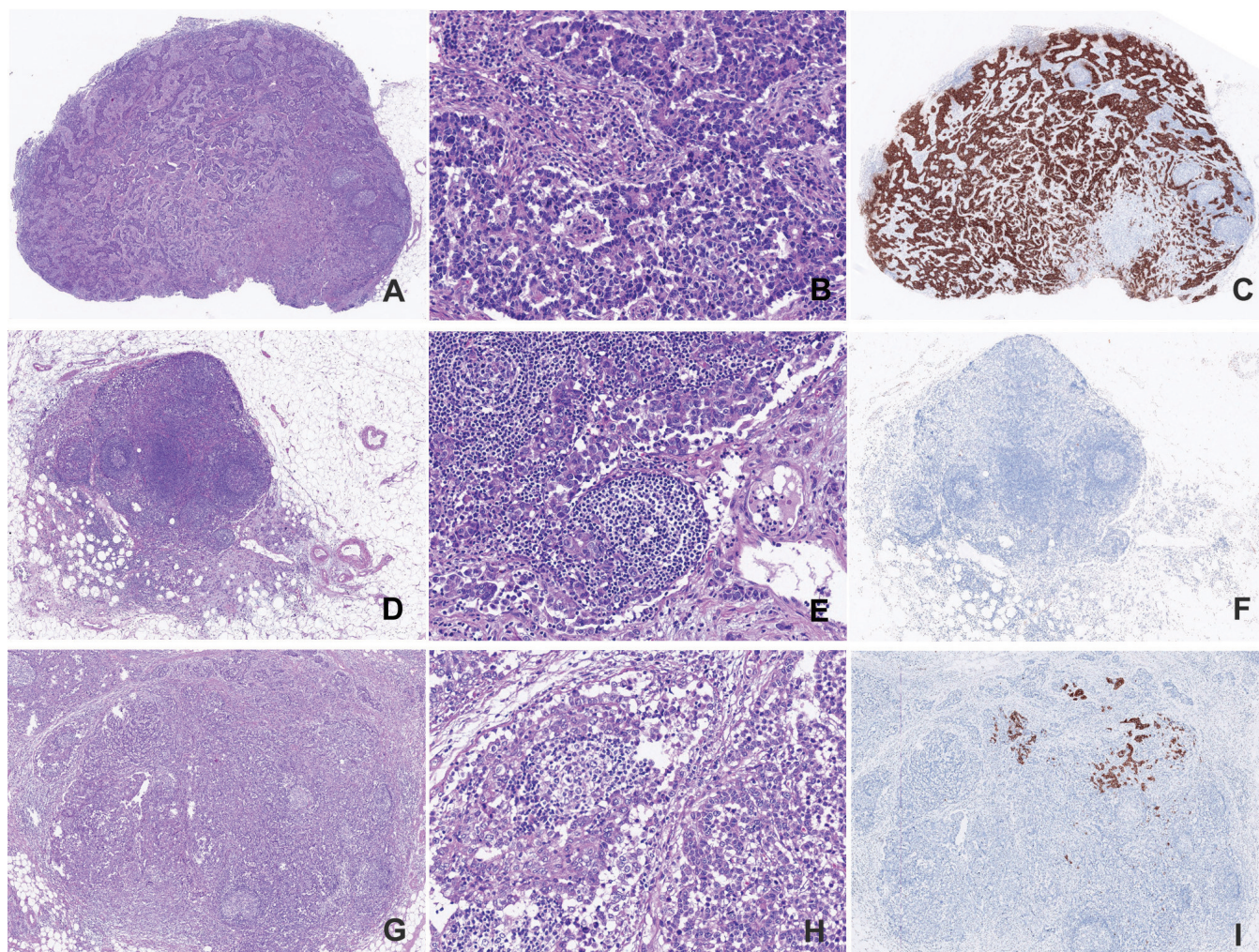


Fig. 3. Three patterns of lymph node metastases. Positive lymph node comprised of pure neuroendocrine component (A, B), or pure glandular component (D, E), or mixed components (G, H). Synaptophysin staining highlighted neuroendocrine components (C, F, I). A, C, D, F, G, I, x 20; B, E, H, x 200.

and second, the possibility that two collision tumors collide and merge in both the primary site and in one lymph node, is extremely low.

In the stomach, the epithelial component could be adenocarcinoma, whereas in the esophagogastric junction, it could be squamous cell carcinoma. The neuroendocrine components of a gastric MANEC usually comprise an NEC, often of large cell type, as in this study (8/10), and rarely an NET, but it could also be small cell type, where the epithelial component is squamous cell carcinoma, located in the esophagogastric junction. However, recent research has suggested that NECs (poorly differentiated) and NETs (well-differentiated) are actually two essentially different types of disease (Domori et al., 2014). Combined with the composite hypothesis, it supports that a real MANEC should be adenocarcinoma mixed with NEC, which shares a more similar pathway alteration with adenocarcinoma, rather than NET. However, a reported case of a mixed tumor with an NET component that metastasized in a mixed pattern challenges this hypothesis (De Luca-Johnson and Zenali, 2016). So, whether these are so-called heterogeneous MANECs that encompass adenocarcinoma and NET is still disputed. Nevertheless, in the 4th edition of the WHO classification of tumors of endocrine organs (2017), this series of tumors was renamed as mixed neuroendocrine-non-neuroendocrine neoplasms (Kloppel et al., 2017).

As defined in the WHO classification of tumors (2010, digestive system, and 2017, endocrine organs), at least 30% of epithelial and neuroendocrine components should be identified to qualify for gastric MANEC or MiNEN (Solcia et al., 2010; Kloppel et al., 2017). However, it is reported that a minor proportion (10-30%) of neuroendocrine differentiation should not be underestimated in gastric mixed carcinomas, because the survival rates of patients with mixed gastric adenocarcinomas with >10% neuroendocrine differentiation were significantly lower than those with <10% (Park et al., 2014). However, a larger series and multicenter study should be carried out to validate the 10% cut-off for the neuroendocrine component in gastric MANEC. Furthermore, how to accurately assess the percentage of the neuroendocrine component in a gastric MANEC should be regulated strictly, avoiding sampling bias.

It is reported that the prevalence of lymphatic and venous involvement and liver metastasis in gastric NECs is higher than in gastric adenocarcinoma (Ishida et al., 2013). Gastric NEC or MANEC has poorer outcome than gastric adenocarcinoma (Jiang et al., 2006; Kubota et al., 2012). There is no significant difference in survival between NEC and MANEC or the presence or absence of adenocarcinoma and/or dysplasia components (Ishida et al., 2013). As to this study, NEC component of primary tumor was more predominant in death cases, than in alive cases group. Moreover, death cases had higher lymph node metastatic rate, and most importantly, NEC component metastasizing to lymph

nodes was more predominant in death cases group than that in alive cases group. These indicate that the NEC component may determine the clinical behavior and outcome in gastric MANEC. Postoperative chemotherapy is needed for most MANECs, because most cases are at an advanced stage when diagnosed. Although it has not been demonstrated in a randomized controlled trial, MANECs with different component metastases may have different responses to chemotherapy (De Mestier et al., 2017). For colorectal MANEC, it is suggested that the treatment strategy should be directed against the aggressive component, which might be decided by the differentiation but not the proportion of each component of the primary tumor (Minaya-Bravo et al., 2015; De Mestier et al., 2017). Since the poorly differentiated NEC component is almost always present in metastases (Li et al., 2011), cisplatin or carboplatin with etoposide are generally recommended as first-line therapy for most MANEC cases, especially for patients with high Ki-67 (>55%) (Garcia-Carbonero et al., 2016). In rare cases, with prominent adenocarcinoma component in metastases, treatment should be similar to "pure" adenocarcinoma (Smith et al., 2014). In the present case series, although 4 patients received postoperative chemotherapy, protocol choosing was variable and challenging, especially for those 2 patients having mixed components of lymph node metastases.

In conclusion, this is the first case series study describing the lymph node metastatic pattern of gastric MANEC (high-grade MiNEN). It supports the composite hypothesis or one stem cell derivation of MANEC, and indicates NEC component may determine the clinical behavior and outcome in gastric MANEC. Furthermore, different metastatic components make the selection of chemotherapy protocol more challenging. A large prospective study on lymph node metastasis of gastric MANEC is needed.

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