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Single Case

Mixed Neuroendocrine Non-Neuroendocrine Neoplasm Arising in the Ectopic Gastric Mucosa of Esophagus

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Keywords

Mixed neuroendocrine non-neuroendocrine neoplasm · Ectopic gastric mucosa · Esophagus · Endoscopic submucosal dissection

Abstract

Esophageal neuroendocrine neoplasms are extremely rare, and their prognosis is poor. Mixed neuroendocrine non-neuroendocrine neoplasms (MiNENs) are even more rare and are defined as tumors consisting of neuroendocrine carcinoma and either adenocarcinoma or squamous cell carcinoma. We report a rare case featuring endoscopic submucosal dissection (ESD) for an esophageal MiNEN, arising from the ectopic gastric mucosa in the lower thoracic esophagus. A 92-year-old male patient was referred to this hospital for investigation of an esophageal tumor. An endoscopic examination revealed a 10 mm elevated lesion, with 8 mm flat areas on the anal side, within the ectopic gastric mucosa located in the lower thoracic esophagus. ESD was carried out, and a histopathological examination revealed a tubular adenocarcinoma composed of differentiated neuroendocrine cells. Immunohistochemical staining was positive for synaptophysin and negative for chromogranin A. The labeling index of Ki-67 was more than 80%. Based on these results, we diagnosed the lesion as an esophageal MiNEN, arising in the ectopic gastric mucosa of the esophagus. The patient remains alive, without recurrence of cancer, 24 months after ESD.

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Introduction

Most esophageal cancers are squamous cell carcinomas (SCCs) or adenocarcinomas. Esophageal adenocarcinomas, arising from Barrett's esophagus in the lower esophagus, are common in western countries. On the other hand, in Asia, most esophageal cancers are SCCs. Esophageal neuroendocrine neoplasms are exceedingly rare and account for only 0.04–1% of all gastroenteropancreatic neuroendocrine tumors (NETs) [1]. Esophageal neuroendocrine neoplasms usually arise from the lower thoracic esophagus, particularly from the Barrett's mucosa, and rarely from the ectopic gastric mucosa [2, 3]. We report an extremely rare case of esophageal mixed neuroendocrine non-neuroendocrine neoplasm (MiNEN) arising from the ectopic gastric mucosa in the lower thoracic esophagus. It is difficult to diagnose MiNENs endoscopically, and this very significant case shows the process of adenocarcinoma development from the ectopic gastric mucosa, with further differentiation into a neuroendocrine carcinoma (NEC), after en bloc resection by endoscopic submucosal dissection (ESD).

MiNENs are defined pathologically as tumors consisting of NEC and either adenocarcinoma or SCC. Each component of a MiNEN accounts for at least 30% of the whole neoplasm. MiNENs have been reported as arising in the digestive system, including the esophagus, stomach, Vater's ampulla, large intestine, and colon [4].

In addition to reporting this case, we reviewed the literature for all previously reported cases of esophageal MiNENs.

Case Report

A 92-year-old man was referred to this hospital for further investigation of an esophageal lesion. His medical history included distal gastrectomy for perforation of a duodenal ulcer, rectal cancer, hypertension, and myocardial infarction. There was no family history of cancer. He had smoked for 40 years and consumed alcohol occasionally. Laboratory tests, including carcinoembryonic antigen (CEA) and SCC antigen, revealed no remarkable abnormalities. Progastrin-releasing peptide (ProGRP) and nonspecific esterase (NSE) were not measured. Esophagogastroduodenoscopy revealed a 10 mm reddish elevated lesion (Fig. 1a), with an 8 mm flat area extending at the anal side (Fig. 1b, arrow). The ectopic gastric mucosa was scattered in the background of the lower thoracic esophageal mucosa (Fig. 1b). A demarcation line between the flat lesion and the background ectopic gastric mucosa was identified by magnifying endoscopy with narrow-band imaging (Fig. 1c). The flat lesions featured an irregular epithelial microsurface and microvascular patterns. The elevated area was covered with the squamous epithelium, and some tumor tissue was exposed from beneath the epithelium (Fig. 1d). A histological examination of the biopsy specimen of the elevated lesion showed a poorly differentiated adenocarcinoma with neuroendocrine differentiation. Submucosal invasion of the tumor was suspected from endoscopic ultrasonography (data not shown). Computed tomography revealed no evidence of the lymph node or distant metastases. Taken together, the pretreatment diagnosis was a poorly differentiated esophageal adenocarcinoma, Lt type 0-I + IIb T1 N0 M0 stage I, according to the TNM classification. Although surgery was considered as a treatment option, we decided to conduct an ESD because of the patient's advanced age. The resected specimen measured 30 × 23 mm and contained elevated (15 × 12 mm) and flat (12 × 8 mm) lesions (Fig. 1e). Histopathologically, the resected specimen contained two distinct components. The oral side of the tumor comprised a NEC, consisting of nests and rosettes of polygonal cells with enlarged round nuclei, and the anal side of the tumor comprised a well-differentiated tubular adenocarcinoma (Fig. 2a, 3a). Furthermore, the transition from tubular adenocarcinoma to NEC was confirmed

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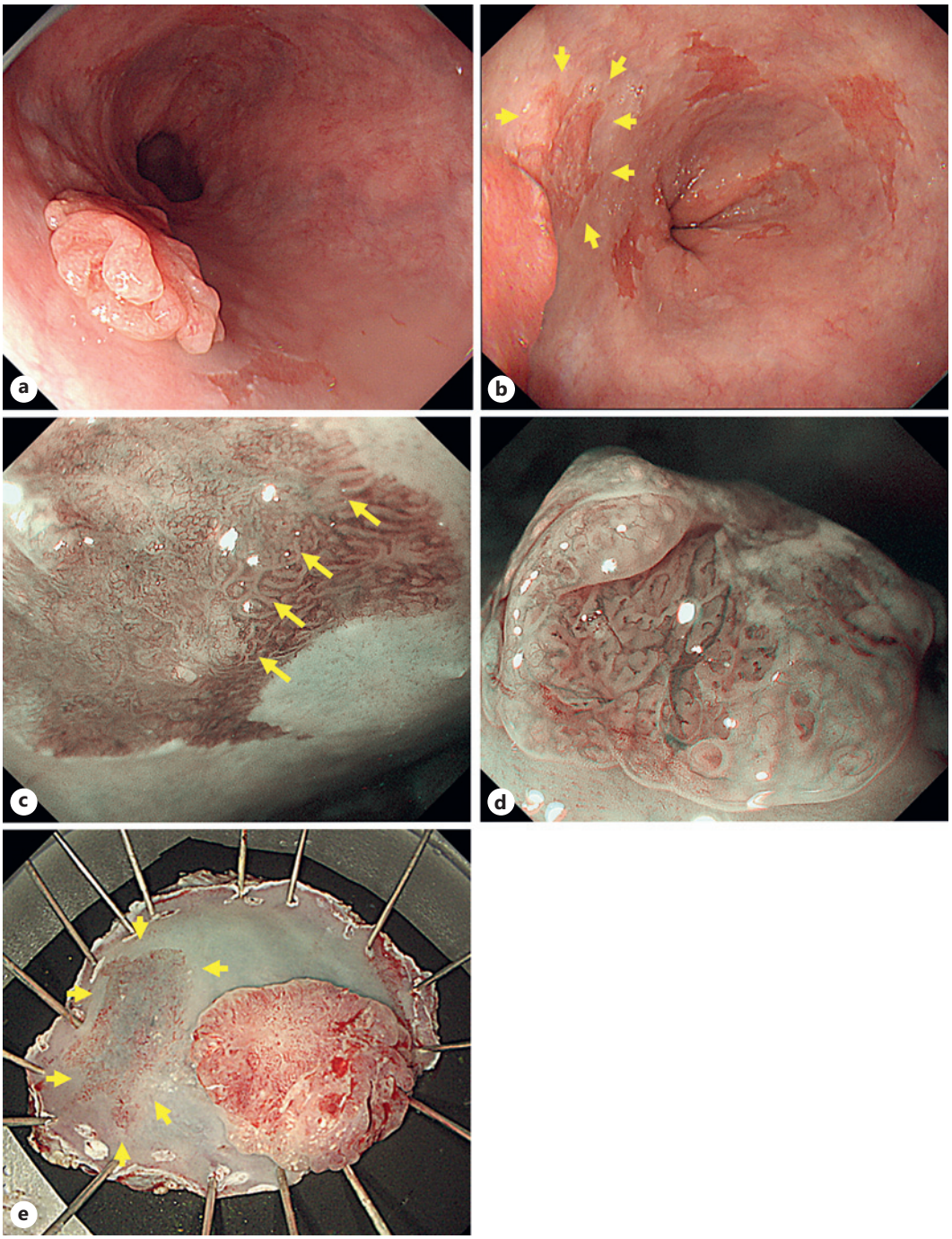

Fig. 1. a Upper gastrointestinal endoscopic findings. **b** Endoscopic examination with white light imaging showed an elevated lesion at the oral side. **c** Magnifying endoscopy with narrow-band imaging (NBI) of the squared area revealed a demarcation line (arrows). **d** The elevated lesions were covered with the squamous epithelium, and some glandular structures with atypical blood vessels were detected. **e** Specimen removed by ESD, 30 × 23 mm in diameter. An elevated lesion (15 × 12 mm) and a flat lesion (12 × 8 mm) were detected in the specimen (arrows).

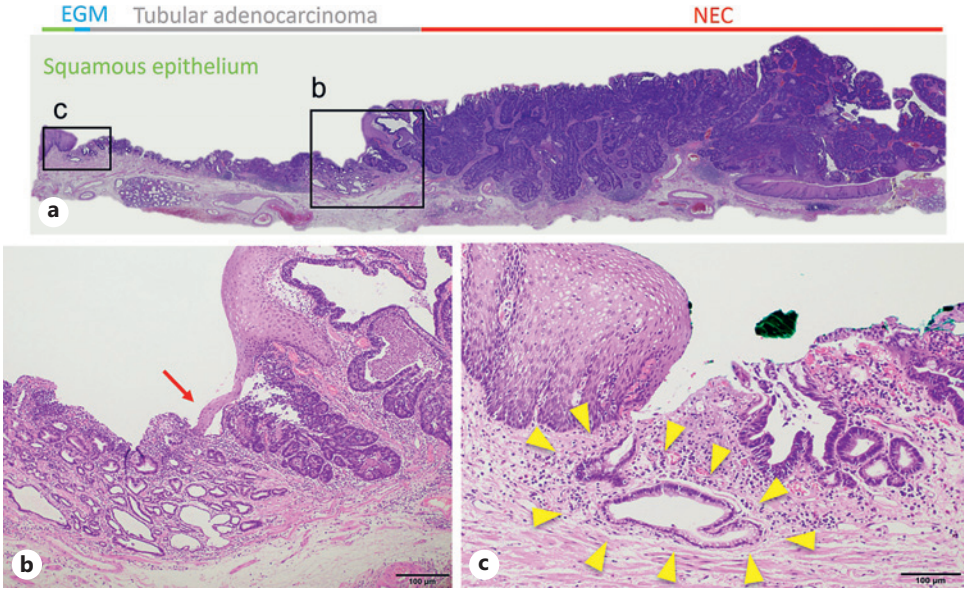

Fig. 2. **a** Pathology image with a loupe. The mapping indicated the relation between NEC, tubular adenocarcinoma, ectopic gastric mucosa (EGM), and squamous epithelium, respectively. **b** Transition from tubular adenocarcinoma to NEC was revealed at ×20 magnification (arrows). **c** The ectopic gastric mucosa was seen in the background mucosa at ×12.5 magnification (arrows).

pathologically (Fig. 2b). The ectopic gastric mucosa was observed between the squamous cell epithelium and the tubular adenocarcinoma. These findings indicate that the tumor had developed from the ectopic gastric mucosa (Fig. 2c). Immunohistochemically, the areas of NECs were positive for synaptophysin and negative for chromogranin A (Fig. 3b, c). A neural cell adhesion molecule (NCAM) was focally positive in the NEC component (Fig. 3d). The two components were contiguous and considered to be one continuous lesion. The adenocarcinoma component accounted for about 35%, while NEC component accounted for about 65% in this tumor. The Ki-67 labeling index was over 80% in the strongest staining region (Fig. 3e). The tumor had spread into the submucosal layer, but vascular and lymphatic invasions were not identified. On the basis of these results, we finally diagnosed the tumor as a MiNEN arising from the ectopic gastric mucosa in the lower thoracic esophagus. The patient has been followed without any signs of recurrence to date, 2 years after the treatment.

Discussion

In 2019, the World Health Organization (WHO) classified esophageal neuroendocrine neoplasms into three subtypes: well-differentiated NETs, poorly differentiated NECs, and MiNENs [5]. Before the classification was made, mixed neoplasms were diagnosed as mixed adenoneuroendocrine carcinomas if each component accounted for less than 30% of the neoplasm [6]. However, to reflect the fact that the non-neuroendocrine components are not adenocarcinomas, or that one or both components are not adenocarcinomas, this category of lesions is now defined as MiNENs.

This is the first report of ESD and a detailed evaluation by immunohistochemistry of a MiNEN arising in the ectopic gastric mucosa of the esophagus. In general, MiNENs do not present characteristic symptoms or endoscopic or imaging findings. It is difficult to make a

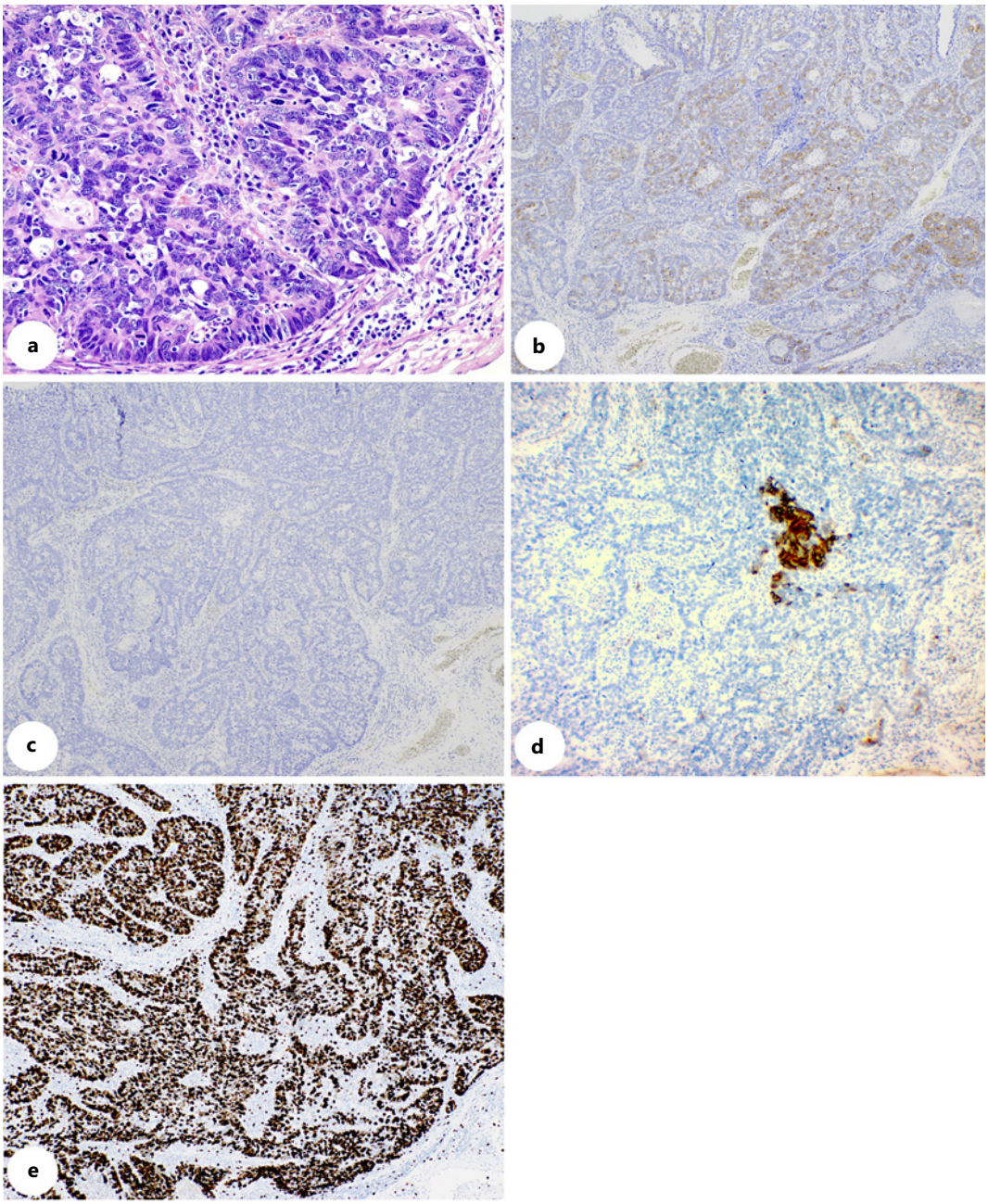

Fig. 3. a Hematoxylin and eosin staining showed cancer cells with a high N/C ratio at ×200 magnification. Immunohistochemical staining at ×100 magnification showed that synaptophysin was positive (**b**), chromogranin A was negative (**c**), CD56 was focally positive (**d**), and the Ki-67 index (**e**) was more than 80%.

definitive diagnosis from a biopsy specimen alone, and the diagnosis is often made by histopathological and immunohistochemical examination of the resected tumor. The World Health Organization defines NECs as positive for endocrine markers such as chromogranin A, synaptophysin, and CD56 [7]. Of these, it has been reported that synaptophysin is the most sensitive marker [8]. Egashira et al. [7] reported that NETs showed strongly positive immunohistochemical staining of chromogranin A, synaptophysin, and CD56 and that ProGRP,

NSE, CEA, and SCC-Ag were detected as tumor markers in 50.0%, 44.4%, 35.7%, and 7.1% of cases, respectively [9].

Only eleven cases of esophageal MiNEN have been reported in the literature [10–13] (Table 1). Ten were in males, with a wide age range. Most of the lesions were located in the esophagogastric junction or the lower thoracic esophagus and some cases were related to Barrett's epithelium. Among these reports, there is only 1 case arising from ectopic gastric mucosa [10]. Generally, the ectopic gastric mucosa of the esophagus occurs in the upper thoracic esophagus, and the MiNENs in the previous reports also had originated in the ectopic gastric mucosa of the upper thoracic esophagus. However, in contrast, in the present case, the MiNEN occurred in the ectopic gastric mucosa of the lower thoracic esophagus. Ten cases (91%) were treated with surgery, and ESD was performed in only 1 case. In the literature, 10 cases of eleven esophageal MiNEN had an adenocarcinoma component [10–13]. On the other hand, Hong et al. [14] reported that 10% of the mixed type of esophageal NEC was composed with adenocarcinoma. We have presumed that these discrepancies were due to the differences in the location of the lesions. The literature we cited includes more lesions in the esophagogastric junction and the lower thoracic esophagus, whereas Hong et al. [14] reported more cases in the middle thoracic esophagus. Positive immunohistochemical staining of synaptophysin and chromogranin A were detected in 91% and 45%, respectively. The median survival time of MiNENs is about 20 months, compared to 8–15 months for pure NECs [5], suggesting that MiNENs have a better prognosis than pure NECs, and the prognosis depends on the degree of Ki-67 proliferation index of the NEC component [9]. The better prognosis of MiNENs than pure NECs may be related to the presence of an adenocarcinoma component in MiNENs [5]. In addition, the fact that MiNENs are detected at a relatively early stage, as has been reported in the past, may contribute to the good prognosis of MiNENs.

Although the carcinogenic pathway of MiNENs has not yet been clarified, two hypotheses have been proposed in previous reports. One is that the originally malignant exocrine cells dedifferentiate and develop into NETs. The other is that monoclonal, multipotent stem cells differentiate into two components [15]. In our case, hematoxylin eosin staining showed a transition from a well-differentiated tubular adenocarcinoma with a glandular duct structure to a NEC with an indistinct glandular duct structure and a solid alveolar shape. Although immunohistochemical staining for synaptophysin was not clearly positive at the site of the well-differentiated tubular adenocarcinoma, we postulate a carcinogenic pathway in which the adenocarcinoma arose from the ectopic gastric mucosa and then the malignant cells differentiated and developed into a NEC. These histological findings are consistent with the hypothesis that exocrine cells, which were originally malignant, dedifferentiated and developed into NETs. Endoscopically, it seemed possible that the well-differentiated tubular adenocarcinoma and NETs originated separately and collided, but the histological findings suggest that it was not so.

No standard treatment for MiNENs has been established because of the rarity of the disease. Basically, the treatment is similar to that for esophageal cancer. Because MiNENs are often found at an advanced stage, surgical treatment is the first choice. As esophageal MiNENs consist of a NEC and an adenocarcinoma component, chemotherapy is primarily recommended for unresectable cases, with a regimen similar to that for a small cell carcinoma of the lung. Endoscopic treatment is an option when the lesion is detected at a relatively early stage, but there have been few reports of endoscopic treatment, and the prognosis after treatment is unknown. As there are few case reports and no established treatment method, it is necessary to select an appropriate treatment in each individual case. Because this patient was elderly and presented at a relatively early stage, we opted for endoscopic treatment. Considering that he survived without recurrence, ESD seems to be a potential treatment option for esophageal MiNENs detected at an early stage.

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Table 1. Summary of esophageal MiNEN from the literature

Case	Author		Age, years	Sex	Location	Background mucosa	Tumor size, mm	Stage	Immunostaining positive	Treatment	Survival, months	Reference
1	Kitajima	2013	64	Male	Ut	Ectopic gastric mucosa	17	T1 N0 M0	CD56, Synaptophysin	Surgery	16 (alive)	Kawazoe 2018 [11]
2	Nakai	2013	63	Male	EGJ	N/A	97	T4 N2 M0	Chromogranin A, NSE	Surgery	24 (alive)	Nakai 2013 [10]
3	Veits	2013	68	Male	EGJ	Barrett's esophagus	N/A	T1 N0 M0	Synaptophysin	ESD	N/A	Kawazoe 2018 [11]
4	Kadhim	2016	68	Male	Lt	N/A	95	T4 N2 M0	Synaptophysin, chromogranin A	Surgery	N/A	Kawazoe 2018 [11]
5	Juanmartin	2017	57	Male	EGJ	N/A	N/A	T3 N3 M0	Synaptophysin, chromogranin A	Surgery	8 (alive)	Kawazoe 2018 [11]
6	Yuan	2017	64	Female	Mt	N/A	40	T2 N2 M0	CD56, synaptophysin	Surgery	8	Kawazoe 2018 [11]
7	Yuan	2017	62	Male	Mt	N/A	30	T2 N2 M0	CD56, synaptophysin	Surgery	9	Kawazoe 2018 [11]
8	Kawazoe	2018	70	Male	EGJ	Barrett's esophagus	25	T1 N0 M0	Synaptophysin	Surgery	4 (alive)	Kawazoe 2018 [11]
9	Yamamoto	2018	81	Male	Lt	N/A	100	T3 N3 M0	Synaptophysin, chromogranin A	Surgery	8	Lim 2020 [13]
10	Mendoza-Moreno	2018	68	Male	EGJ	N/A	N/A	T3 N3 M0	Synaptophysin, chromogranin A	Surgery	N/A	Mendoza 2018 [12]
11	Lim	2020	67	Male	Lt	Barrett's esophagus	N/A	T1 N0 M0	Synaptophysin	Surgery	N/A	Lim 2020 [13]
12	Present case		92	Male	Lt	Ectopic gastric mucosa	27	T1 N0 M0	Synaptophysin	ESD	24 (alive)	

ESD, endoscopic submucpsal dissection; EGJ, esophago-gastric junction; LN, lymph node; Lt, lower thoracic esophagus; Mt, middle thoracic esophagus; N/A, non-applicable; Ut, upper thoracic esophagus; NSE, nonspecific esterase.

In conclusion, this case report documents an esophageal MiNEN arising from the ectopic gastric mucosa in the lower thoracic esophagus. This is the first report of ESD and a detailed evaluation by immunohistochemistry of a MiNEN arising in the ectopic gastric mucosa of the esophagus. It was difficult to make an accurate preoperative diagnosis based on biopsy specimens and endoscopic findings, and the diagnosis of this type of lesion should be made by immunohistochemistry, such as for chromogranin A and synaptophysin.

The CARE Checklist has been completed by the authors for this case report and is attached as online supplementary material (for all online suppl. material, see www.karger.com/doi/10.1159/000527699).

Statement of Ethics

This study was conducted according to the World Medical Association Declaration of Helsinki: ethical principles for medical research involving human subjects. A written informed consent was obtained from the patient for publication of the details of his medical case and any accompanying images. This study protocol was reviewed and the need for approval was waived by the Ethics Committee of Kumamoto University Hospital.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

Ryosuke Gushima wrote the manuscript and made the pathological diagnosis. Hideaki Miyamoto, Miyuki Imamura, and Takayoshi Sonoda performed the endoscopic examinations and managed the patient. Kenshi Matsuno, Akira Yamasaki, and Yoki Furuta participated in the diagnosis. Shunpei Hashigo, Masakuni Tateyama, and Yasuhito Tanaka revised the manuscript. Hideaki Naoe wrote and revised the manuscript.

Data Availability Statement

All data generated or analyzed during this study are included in this article and its online supplementary material. Further inquiries can be directed to the corresponding author.

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