Endoscopic Submucosal Dissection for Early-Stage Neuroendocrine Carcinoma of The Esophagus：A Case Report

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Case report

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Endoscopic submucosal dissection for Early-stage Neuroendocrine Carcinoma of the Esophagus：A Case Report

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Abstract

Background: Neuroendocrine carcinoma (NEC) of the esophagus is rare, highly aggressive and lacks biological features.

Case presentation: In this report, we describe a patient with Esophageal NEC who was successfully treated using endoscopic submucosal dissection (ESD). A 55-year-old woman presented with intermittent mild dysphagia for 2 months. Gastroscopy revealed a disc-shaped protruding lesion about 18mm×18mm in size on the upper esophagus, 25cm from the incisors. Endoscopic ultrasonography (EUS) demonstrated the bulged lesion was highly echoic and homogeneous, originating from the muscularis mucosa. We assessed en bloc resection by ESD for therapeutic diagnosis to be a safe and appropriate treatment. The tumor was removed using ESD. Histopathological examination revealed a poorly differentiated neoplasm comprising large cells with marked nuclear atypia and multifocal necrosis Immunohistochemistry staining revealed tumor tissue that was positive for Ki67, CgA, Syn, CD56, but negative for P40, P63, S-100 protein. These histopathological results were consistent with a diagnosis of esophageal NEC, large cell type, derived from the muscularis mucosae. After

comprehensive consideration, we adopted the combination treatments (ESD plus an adjuvant chemotherapy). The patient has been followed up till now with no recurrence.

Conclusions: En bloc resection approach by ESD play a vital role in the early therapeutic diagnosis of esophageal NEC.

Key words: esophagus, neuroendocrine, carcinoma, endoscopy, dissection

Background

Neuroendocrine carcinoma (NEC) of the esophagus is extremely rare with an incidence ranging from 0.01 to 0.08 cases per 100,000 persons per year [1], aggressive tumor that lacks biological features. Currently, there is still a lack of large sample clinical epidemiological studies approaching this issue. The early diagnosis of esophageal NEC is difficult due to the absence or late onset of symptoms.

Hence, most cases were diagnosed at late stages (III and IV) according to AJCC 8th edition, and had low survival rates, with the median overall survival of about 11.3 months[2], but the cases with long term survival after surgical resection were not excluded[3]. Nowadays, diagnosis is usually dependent on endoscopy and pathology, with histological diagnosis made via immunohistochemical staining of common neuroendocrine markers, i.e. Ki67, chromogranin A (CgA), synaptophysin (Syn), cytokeratin (CK), and lymphocyte antigen 56 (CD56) [4-6]. If the early diagnosis and histological complete resection can be achieved, the survival of this disease will be further improved. Herein, we report a case of early-stage NEC of the esophagus treated by endoscopic submucosal dissection (ESD).

Case presentation

A 55-year-old woman presented with intermittent mild dysphagia for 2 months. The patient had a normal appetite, no weight loss, no nausea or vomiting. Her symptoms often occurred when consuming dry foods that induced mild dysphagia. However, her condition immediately improved without any medical intervention. She had no prior history of esophageal surgery. Physical examinations were normal. Laboratory data were within normal range, including total bilirubin, direct bilirubin, C-reactive protein (CRP), alpha-fetoprotein (AFP), carcinoembryonic antigen (CEA), carbohydrate antigen 19-9 (CA199), neuron specific enolase (NSE), and fecal occult blood test (FOBT) results. Chest enhanced computed tomography was normal, while abdominal computed tomography revealed a hepatic cyst and renal calculus.

Gastroscopy revealed a disc-shaped protruding lesion about 18mm×18mm in size on the upper esophagus, 25cm from the incisors (Fig. 1a). Endoscopic ultrasonography (EUS) with a 20-MHz catheter probe demonstrated the bulged lesion was highly echoic and homogeneous, originating from the muscularis mucosa (Fig. 1b).

Gastroscopy and EUS showed that the tumor was confined to the submucosa and was less than 11-20 mm in size. No radiographic evidence of lymph node enlargement and distant metastasis was found. Hence, we assessed en bloc resection by ESD to be a safe and appropriate treatment. The edge of the protruding lesion was marked intraoperatively. We proceed with the submucosal injection of indigo-carmine diluted with normal saline solution to create a submucosal lifting (Fig.2a). The lesion was

completely removed using dual knife with a step-by-step electrocauterization (Fig.2b), metal clips were applied to close the mucosal gap (Fig. 2c). Tumor samples were taken out using a net basket and sent for pathological examination. Dissection time was 14 min. The patient started with a liquid diet in 72h later after the dissection, and she was discharged from hospital 5 days later to confirm the absence of complications.

Macroscopically, the resected specimen was a gray and white mucosal tissue, with nodules of 9 × 8 × 8mm observed under the mucosa having a tough texture (Fig.2d). Histopathological examination revealed a poorly differentiated neoplasm comprising large cells with marked nuclear atypia, multifocal necrosis and twenty mitotic figures per 10 high-power fields (Fig.3a, b). Both horizontal and vertical margins of resection were negative. Immunohistochemistry staining revealed tumor tissue that was positive for the following markers: Ki67 (80%+), CgA, Syn, CD56, cytokeratin (AE1/AE3), and negative for P40, P63, S-100 protein (Fig.3c, d). These findings are consistent with a diagnosis of esophageal NEC derived from the muscularis mucosae. Negative lympho-vascular invasion was also confirmed with immunohistochemical staining of CD31, CD240 (Fig.3e, f).

According to the immunohistochemistry staining results, the tumor was evaluated as large cell esophageal carcinoma (LCEC), Grade3, limited disease (LD)/T1aN0M0 stage. Based on type, grade and stage of the tumor, we finally decided to add adjuvant EP regimen chemotherapy (Etoposide 60mg/m^2 days1-5+ Cisplatin 25mg/m^2 days1-3, repeat cycle every 3 weeks for 6 cycles) after ESD surgery. The patient remains

disease free as of the 15-months follow up, with no evidence of local or metastatic recurrence.

Discussion

Esophageal NEC is a poorly differentiated, highly malignant tumor consisting of small or medium to large cells with significant nuclear atypia, multifocal necrosis, and mass mitosis (> 20/10 high power field)[7].

Gross examinations of esophageal NECs have shown a wide variety of features, including submucosal polypoid infiltrating growths that are often covered by normal epithelium, or ulcerative nodules on the surface of the esophagus mucosa. Microscopically, neuroendocrine tumor cells are arranged in nests with trabecular growths surrounded by palisades and rosettes. The frequency of lymphatic, venous and peripheral nerve invasions is high [8].

Immunohistochemistry staining of Syn, CgA and NSE are usually positive in NETs, where Syn is the most sensitive marker. NETs usually have Ki-67 index >20%. In addition, AE1/AE3, cytokeratin 34bE12 (CK34bE12), CD56, thyroid transcription factor-1 (TTF-1) and cytokeratin 10/13 staining should also be detected in NETs[9].

Although the incidence is low, primary esophageal NETs are still relatively easy to detect using routine gastroscopy. At present, an increasing number of esophageal NETs are diagnosed early by endoscopy (tumor size less than 11-20 mm and confined to the mucosa/submucosa). Due to the low frequency of lymph node and distant metastasis, local resection (including endoscopic treatment) could be performed. Endoscopic resection is a minimally invasive treatment for patients with esophageal

NETs. For our patient, we performed ESD resection of the esophageal NEC and histologically achieved complete resection. ESD has an excellent resection rate and can provide histological grading in order to guide subsequent treatment decisions. If the tumor cannot be completely resected, additional surgery or systemic chemoradiotherapy will be required. To a certain extent, complete resection of the tumor could prevent excessive treatment burden. However, endoscopic treatment for relapsing remnant tumor may be difficult due to the presence of fibrotic tissue hampering the separation of tumor from the intrinsic muscularis. Studies have demonstrated that ESD treatment could reduce the incidence of this outcome due to complete histological resection[10].

Conclusions

In conclusion, no standard treatment strategies are available for esophageal NEC due to a lack of evidence. En bloc resection approach by ESD play a vital role in the early therapeutic diagnosis of esophageal NEC.

Abbreviations

NEC: Neuroendocrine carcinoma
ESD: endoscopic submucosal dissection
EUS: Endoscopic ultrasonography
CgA: chromogranin A
Syn: synaptophysin
CK: cytokeratin
CD56: lymphocyte antigen 56
CRP: C-reactive protein
AFP: alpha-fetoprotein
CEA: carcinoembryonic antigen
CA199: carbohydrate antigen 19-9
LCEC: large cell esophageal carcinoma
LD: limited disease

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Authors' contributions

All authors participated in the patient's care. ZF performed the surgeries described in this report. ZHC constructed the conception and design of this report. NT prepared the draft of the manuscript. All authors read and approved the final manuscript.

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Availability of data and materials

All data generated or analyzed during this study are included in this published article.

Ethics approval and consent to participate

Not applicable

Consent for publication

The patient provided written consent to publish this case report.

Competing interests

The authors declare that they have no competing interests.

Conflict of interests

Authors declare no conflict of interests for this article.

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Figures

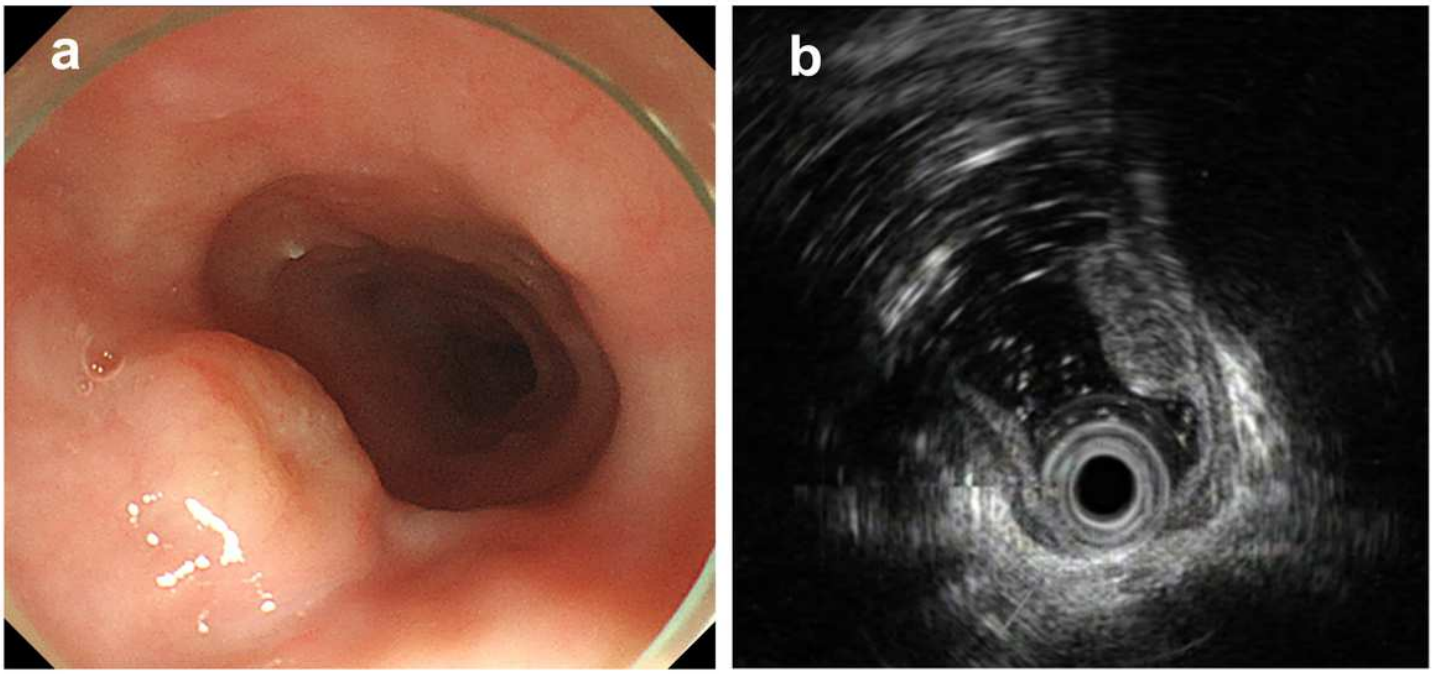

Figure 1

Gastroscopy revealed a disc-shaped protruding lesion about 18mm×18mm in size on the upper esophagus, 25cm from the incisors (Fig. 1a). Endoscopic ultrasonography (EUS) with a 20-MHz catheter probe demonstrated the bulged lesion was highly echoic and homogeneous, originating from the muscularis mucosa (Fig. 1b).

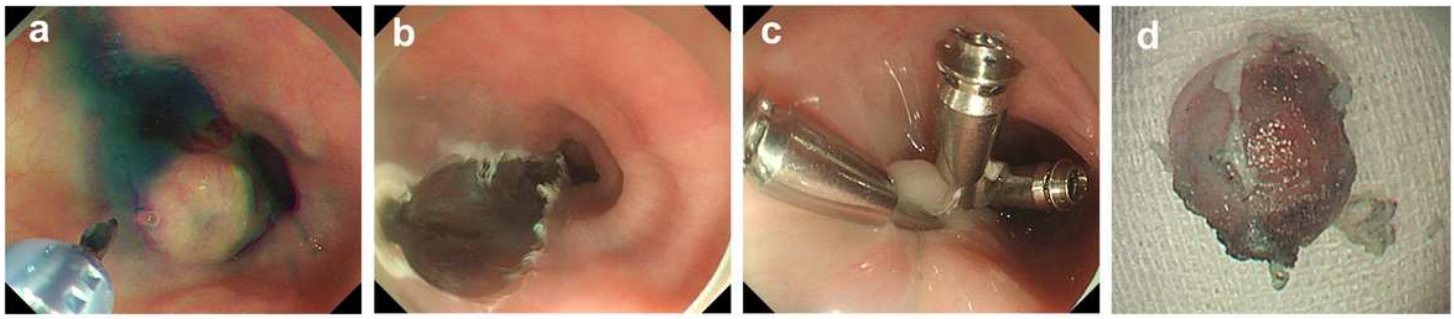

Figure 2

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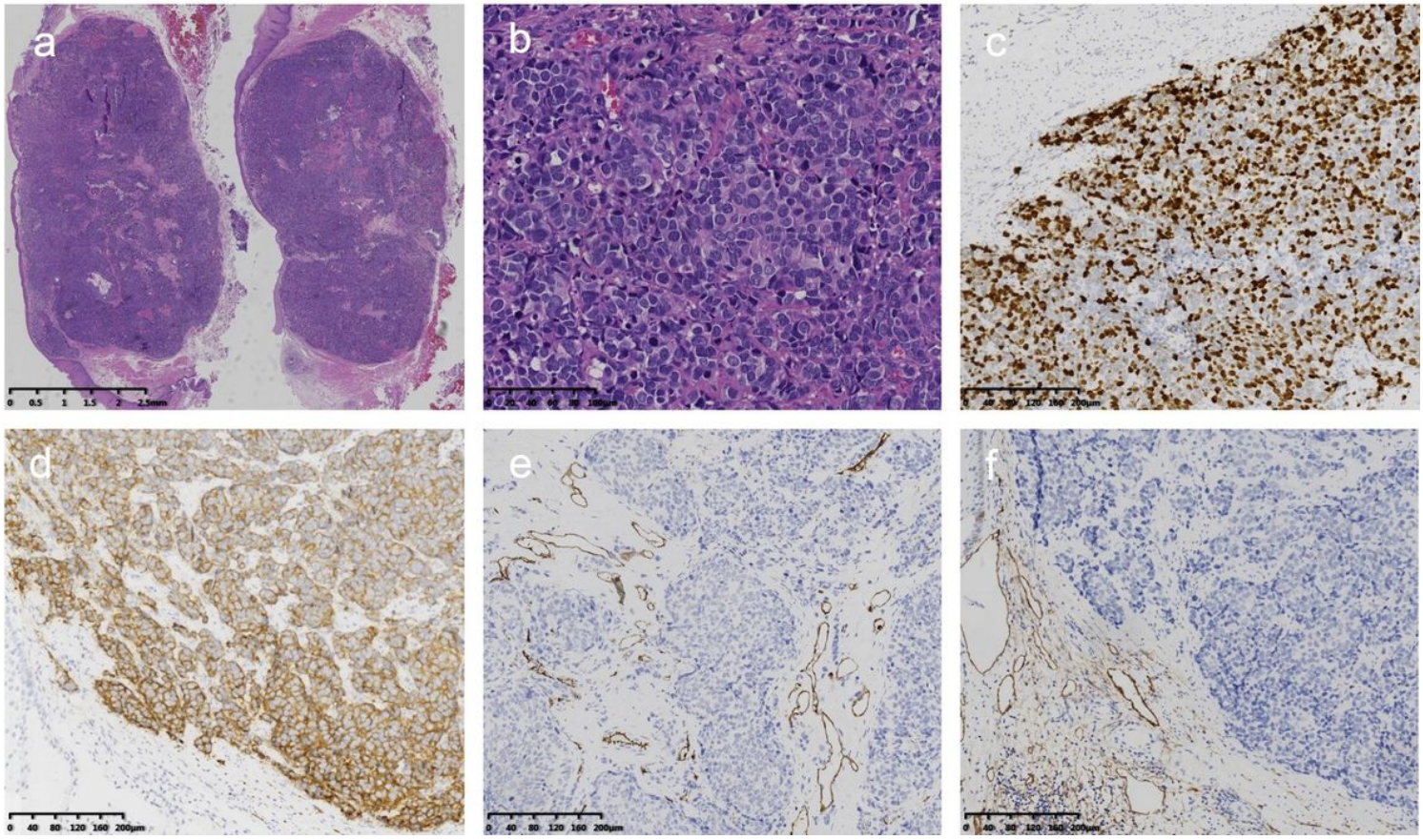

Figure 3

Histopathological examination revealed a poorly differentiated neoplasm comprising large cells with marked nuclear atypia, multifocal necrosis and twenty mitotic figures per 10 high-power fields (Fig.3a, b). Both horizontal and vertical margins of resection were negative. Immunohistochemistry staining revealed tumor tissue that was positive for the following markers: Ki67 (80%+), CgA, Syn, CD56, cytokeratin (AE1/AE3), and negative for P40, P63, S-100 protein (Fig.3c, d). These findings are consistent with a diagnosis of esophageal NEC derived from the muscularis mucosae. Negative lympho-vascular invasion was also confirmed with immunohistochemical staining of CD31, CD240 (Fig.3e, f).