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

Two-year follow-up of NEC.

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Abstract

BACKGROUND

Neuroendocrine carcinoma (NEC) of the esophagus is rare, highly aggressive, and lacks biological features. Currently, there are no established standard treatments for this cancer. In this report, we describe a patient with large-cell NEC of the esophagus who was successfully treated using endoscopic submucosal dissection (ESD) combined with adjuvant chemotherapy.

CASE SUMMARY

A 55-year-old woman presented with intermittent mild dysphagia for 2 mo. Gastroscopy revealed a disc-shaped protruding lesion about 18mm×18mm in size on the upper esophagus. Endoscopic ultrasonography (EUS) demonstrated the bulged lesion originated from the muscularis mucosa. We assessed en bloc resections using ESD for therapeutic diagnosis to devise a safe and appropriate treatment. Histopathological examination revealed a poorly differentiated neoplasm comprising of large cells with marked nuclear atypia and multifocal necrosis. In addition, the specimens had a negative horizontal margin and vertical margins. Depth of invasion was classified as submucosa 2 (SM2) without lymphovascular invasion. These histopathological results were consistent with a diagnosis of esophageal NEC, large cell type. Adjuvant therapy has been considered for ESD patients with SM2/SM3 Lesions and patients with poorly differentiated lesions. After comprehensive consideration, we initiated combination treatment, i.e., ESD plus adjuvant chemotherapy. The patient remains disease-free as of the 2-year follow-up period.

CONCLUSION

En bloc resection approach using ESD may play a vital role as therapy and a diagnostic modality for esophageal NEC.

Key Words: esophagus; neuroendocrine carcinoma; endoscopy; dissection; case report

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Core Tip: we describe a patient with large-cell neuroendocrine carcinoma (NEC) of the esophagus who was successfully treated using endoscopic submucosal dissection (ESD) combined with adjuvant chemotherapy. No standard treatment strategies are available for esophageal NEC due to a lack of clinical studies and its rarity. En bloc resection approach using ESD may play a vital role as therapy and a diagnostic modality for esophageal NEC.

INTRODUCTION

Neuroendocrine carcinoma (NEC) of the esophagus is extremely ² rare with an incidence ranging from 0.01 to 0.08 cases per 100,000/year [1]. This is an aggressive tumor that lacks biological features. Poorly differentiated NECs are of either small cell or large cell cytology. The former is the dominant histological type and only 10% of NECs are classified as large cell cytology [2].

Currently, there is a lack of clinical epidemiological studies that have been performed with no established standard treatment [3-4]. The early diagnosis of esophageal NEC is difficult due to the absence or late onset of symptoms. Hence, most cases are diagnosed at late stages (III and IV) based on the AJCC 8th edition. This accounts for the low survival rates, with the median overall survival of about 11.3 mo [5], however, cases with long-term survival after surgical resection were not excluded [6]. Diagnosis usually relies 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) [7-9]. Patient survival would be improved if early diagnosis and histological complete resection could be achieved [10]. Herein, we report a case of large-

cell NEC of the esophagus treated using endoscopic submucosal dissection (ESD) at its early stage.

CASE PRESENTATION

Chief complaints

A 55-year-old woman presented with intermittent mild dysphagia for 2 mo.

History of present illness

The patient had a normal appetite, no weight loss, no nausea or vomiting. Her symptoms often occurred when consuming dry food that induced mild dysphagia. The symptoms were initially noticed 2 mo before evaluation.

History of past illness

The patient had no prior history of esophageal surgery. There was no history of diabetes mellitus, hypertension, stroke, or coronary artery disease.

Personal and family history

The patient acknowledged no relevant family history of cancer.

Physical examination

No obvious abnormalities were found on physical examination.

Laboratory examinations

Laboratory data were within normal ranges, including ⁴total bilirubin, direct bilirubin, C-reactive protein (CRP), carcinoembryonic antigen (CEA), carbohydrate antigen 19-9 (CA199), and neuron-specific enolase (NSE).

Imaging examinations

Chest enhanced computed tomography was normal, while abdominal computed tomography revealed a hepatic cyst and renal calculus. There was no evidence of

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

FINAL DIAGNOSIS

The final diagnosis of the presented case was neuroendocrine carcinoma of the esophagus.

TREATMENT

Gastroscopy and EUS showed that the tumor was confined to the muscularis mucosae. No radiographic evidence of lymph node enlargement and distant metastasis was found. Hence, we assessed en bloc resection using ESD for confirmation and determine the appropriate treatment. The edge of the protruding lesion was marked intraoperatively. We proceeded with a submucosal injection of indigo-carmin diluted with normal saline solution to create a submucosal lifting (Figure 2A). The lesion was completely removed using a dual knife with step-by-step electrocauterization (Figure 2B). Afterward, metal clips were used to close the mucosal gap (Figure 2C). Tumor samples were sent for pathological examination. Dissection time was 14 min. The patient was started on a liquid diet 72h post dissection. After monitoring for complications, the patient was discharged from hospital 5 days later.

OUTCOME AND FOLLOW-UP

Macroscopically, the resected specimen was a gray and white mucosal tissue, with nodules of 9 × 8 × 8mm observed under the mucosa and having a tough texture (Figure 2d). Histopathological examination revealed a poorly differentiated neoplasm comprising of large cells with marked nuclear atypia, multifocal necrosis, and twenty mitotic figures per 10 high-power fields. Both horizontal and vertical margins of

resection were negative (Figure 3A, C). Depth of invasion was classified as submucosa 2 (SM2, submucosal invasion $\geq 200 \mu\text{m}$) (Figure 3B). 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 (Figure 3D, F). Lymphovascular invasion was also ruled out using immunohistochemical staining with CD31 and CD240 (Figure 3G, H).

Based on the immunohistochemistry staining results, the tumor was classified as large cell esophageal carcinoma (LCEC), Grade3, and limited disease (LD)/T1aN0M0 stage. Currently, the therapeutic strategy for NEC of the esophagus has still not been established. The National Comprehensive Cancer Network (NCCN) guidelines Version 3.2018 recommends that resectable large cell neuroendocrine carcinomas should be treated by resection and chemotherapy with or without radiotherapy^[11]. Based on the type, grade, and stage of this tumor, ESD may be considered as the primary treatment modality for mucosal lesions. Adjuvant therapy has been considered for ESD patients with SM2/SM3 Lesions and patients with poorly differentiated lesions ^[12-13]. Based on careful consideration, we decided to include adjuvant EP regimen chemotherapy (Etoposide 60mg/m² days1-5+ Cisplatin 25mg/m² days1-3, repeat cycle every 3 wk for 6 cycles) after ESD surgery. The patient was closely followed up every 3 mo for 2 years to date. CT scans did not identify regional lymphadenopathy or distant metastasis during follow-up.

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) ^[14-15].

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 are high [16].

Immunohistochemistry staining for NETs are usually positive for Syn, CgA, and NSE, where Syn is the most sensitive marker. NETs usually have a Ki-67 index >20%. In addition, AE1/AE3, cytokeratin 34bE12 (CK34bE12), CD56, thyroid transcription factor-1 (TTF-1) and cytokeratin 10/13 staining are also observed in NETs [17-18].

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) is the treatment option. Endoscopic resection is a minimally invasive treatment for patients with esophageal NETs. ESD has an excellent resection rate and can provide histological grading to guide subsequent treatment decisions. If the tumor cannot be completely resected, additional surgery or systemic chemoradiotherapy will be required [19]. For our patient, we performed ESD resection of the esophageal NEC. Although the specimens had a negative horizontal margin and vertical margins without lymphovascular invasion, depth of invasion was classified as SM2. Adjuvant therapy has been considered for ESD patients with SM2/SM3 Lesions and patients with poorly differentiated lesions. To a certain extent, complete resection of the tumor could prevent excessive treatment burden. However, endoscopic treatment for relapsing remnant tumors 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 [20].

CONCLUSION

In conclusion, no standard treatment strategies are available for esophageal NEC due to a lack of clinical studies and its rarity. En bloc resection approach using ESD may play a vital role as therapy and a diagnostic modality for esophageal NEC.

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