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[Case Report]

A CASE OF ENDOCRINE CELL CARCINOMA COMBINED WITH SQUAMOUS CELL CARCINOMA OF THE ESOPHAGUS RESECTED BY ENDOSCOPIC SUBMUCOSAL DISSECTION

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Abstract : A 55-year-old man with esophageal carcinoma received endoscopic submucosal dissection (ESD) in en-bloc resection. Histopathological examination revealed an admixture of squamous cell carcinoma (SCC) and endocrine cell carcinoma (ECC) with invasion of the deep submucosa. Immunohistochemically, CD 56 and chromogranin A were positive for ECC. Small-cell, medium-cell, and large-cell type ECC were partly surrounded with SCC and partly formed the duct, presenting various patterns. After ESD, he received chemotherapy including CPT-11 plus Cisplatin. He is alive and in good condition today, 55 months after ESD, with no evidence of recurrence.

Key words : endocrine cell carcinoma (ECC), endoscopic submucosal dissection (ESD), esophageal cancer, narrow band imaging (NBI), combined cancer

INTRODUCTION

Endocrine cell carcinoma (ECC) of the esophagus is a rare disease. The clinical feasibility of local endoscopic treatment (e.g., endoscopic mucosal resection, EMR; endoscopic submucosal dissection, ESD) for superficial esophageal ECC has not been established because it is often discovered in the advanced stage¹⁾. This report describes a case of superficial esophageal ECC combined with squamous cell carcinoma (SCC) treated with ESD.

CASE REPORT

A 55-year-old man came to our hospital after an esophageal tumor had been discovered by esophagogastroduodenoscopy (EGD). He had smoked two packs of cigarettes per day for 20 years. He had taken drugs for diabetes mellitus. Blood tests revealed no abnormality except for a high value of

HbA1c (10.3%). The serum SCC antigen level was 0.9 ng/ml, which was within normal limits. EGD revealed a 30-mm reddish depressed lesion with a central elevation in the middle thoracic esophagus (Fig. 1a). A biopsy specimen from this lesion revealed SCC histologically. Narrow band imaging (NBI) endoscopy of the lesion showed a brownish area (Fig. 1b). Magnifying endoscopy with NBI revealed intra-epithelial papillary loop (IPCL) type V-1 and type V-2 in the depressive area (Fig. 1c), and IPCL type V-3 in IPCL classification by Inoue²⁾ in the elevated area (Fig. 1d), but it revealed no type 4R vessels corresponding to poorly differentiated carcinoma or specific histologic type of carcinoma in classification of microvascular pattern by Arima *et al.*³⁾ IPCL type V-3 showed that the depth of tumor invasion was the muscularis mucosa or slight submucosa. Computer tomography (CT) of the chest and abdomen showed neither lymph node nor distant metastasis. Endoscopic ultrasonography

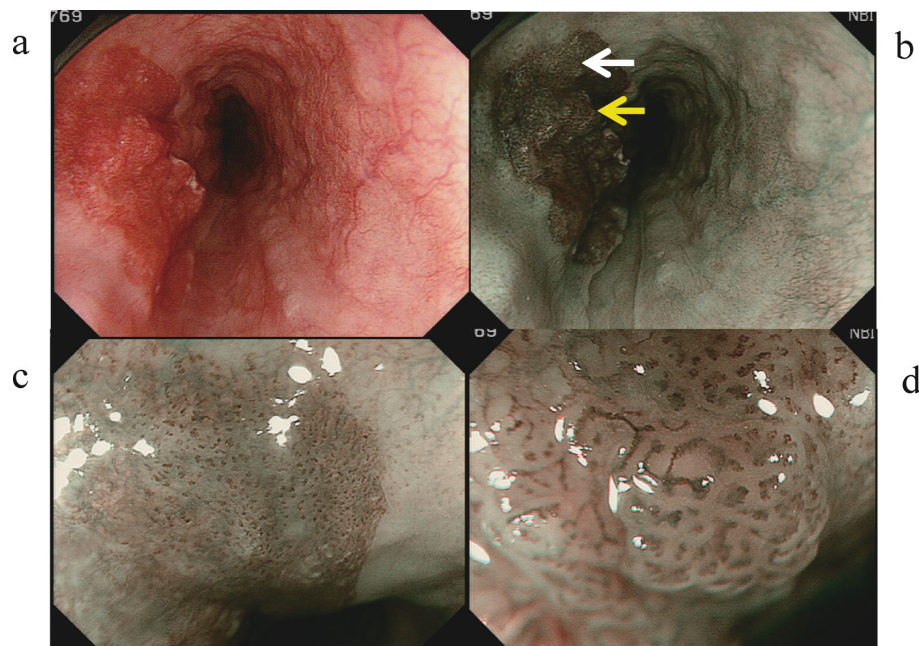


Fig. 1. Endoscopic findings of the lesion.

a) White light imaging revealed a 30-mm reddish depressed lesion with a central elevation in the middle thoracic esophagus. b) Narrow band imaging (NBI) endoscopy revealed a brownish area. The white arrow indicates a depressive area. The yellow arrow indicates an elevated area. c) Magnifying endoscopy with NBI revealed intra-epithelial papillary loop (IPCL) type V-1 and V-2 in IPCL classification by Inoue in the depressive area (white arrow in Fig. 1a). d) Type V-3 in IPCL classification by Inoue in the elevated area (yellow arrow in Fig. 1a).

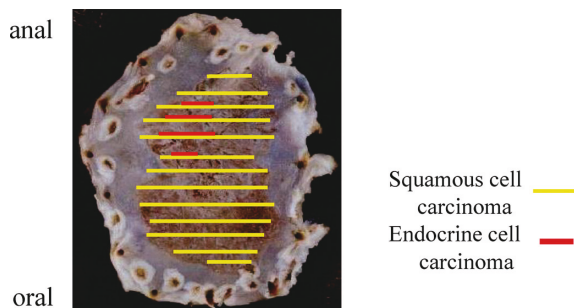


Fig. 2. Resected specimen by endoscopic submucosal dissection.

The fixed resected specimen is mapped by yellow and red lines (yellow lines, squamous cell carcinoma; red lines, endocrine cell carcinoma). Endocrine cell carcinoma exists in the elevated area.

(EUS) was not performed because the patient did not consent. We recommended surgery or chemoradiotherapy because the tumor depth was suspected to extend to the submucosa and because it presented the possibility of lymph node metastasis. However, he rejected each treatment, so ESD was performed using a single-channel gastroscope (GIF-Q260J; Olympus Medical Systems Corp., Tokyo, Japan) and an electrosurgical unit (ICC-200; Erbe Elektromedizin GmbH, Tübingen, Germany) after informed consent was obtained. An electrosurgical

knife (Dual knife; Olympus Medical Systems Corp., Tokyo, Japan) was used with electrosurgical hemostatic forceps (Coagrasper; Olympus Medical Systems Corp., Tokyo, Japan). Hyaluronic acid (MucUp; Johnson & Johnson, Tokyo, Japan) was used to create a submucosal fluid cushion. No complication was found during or after ESD.

The lesion was resected en-bloc by ESD. Histopathological examination of ESD specimens revealed an admixture of ECC combined with SCC with invasive depth of the deep submucosa (Figs. 2, 3a). Immunohistochemical analysis revealed that CD56 (Figs. 4a and 4b) and chromogranin A were positive for ECC. Synaptophysin was negative. This lesion was classified into grade 3 according to the WHO neuroendocrine tumor classification in 2010, because its Ki-67 index was 75.7%. Small-cell type, mediate-cell type, and large-cell type ECC were arranged in sheet fashion, existing mainly in the submucosa mixed with moderately differentiated SCC (Fig. 3b). The ECC was partly surrounded by SCC (Fig. 3c), partly forming a duct (Fig. 3d) and presenting various patterns. The SCC bordering the ECC and the SCC surrounded by the ECC remained moderately differentiated. Their levels of differentiation remained unchanged. No clear transition from SCC to ECC was found. Lymphovascu-

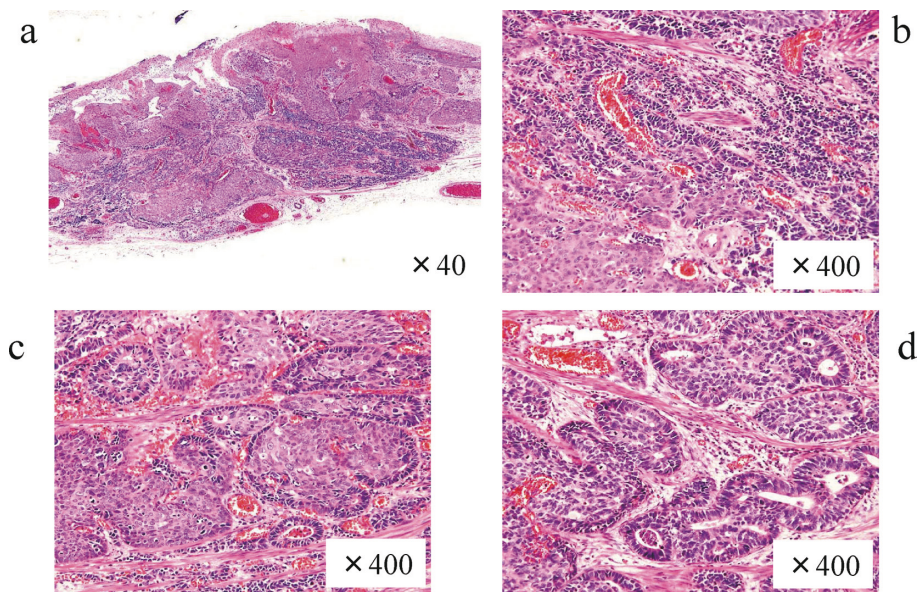


Fig. 3. Histological examination of resected specimens (hematoxylin and eosin staining).

- a) Low-power view, mixed with squamous, small cell type, mediate cell type, and large cell type endocrine cell carcinoma (ECC). ECC exists mainly in the submucosa.
- b) High-power view shows ECC arranged in sheet fashion mixed with squamous cell carcinoma (SCC).
- c) ECC is surrounded by SCC.
- d) ECC formed a duct formation.

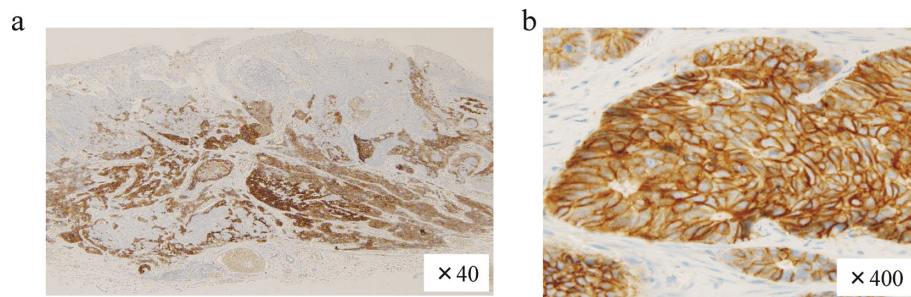


Fig. 4. Immunohistochemical staining.

Immunohistochemically obtained results showed that CD56 were positive for endocrine cell carcinoma : a) low-power view and b) high-power view.

Table 1. Esophageal endocrine cell carcinoma conducted by endoscopic resection (ER)

Author	Diagnosis before ER	Invasion depth	Treatment after ER	Prognosis, Period (month)
Takeshita	Malignant small round cell tumor	Muscularis mucosa	Etoposide and carboplatin	Alive, no recurrence, 28
Kobayashi	SCC	Shallow submucosa	5-FU and cisplatin surgery, radiation docetaxel, 5-FU, and cisplatin	Dead, 25
Ozawa	Undifferentiated cancer for which it is not possible to determine whether it is SCC or not	Shallow submucosa	CPT-11 and cisplatin	Alive, abdominal lymph node metastasis relapse, 6
Tokunaga	Without biopsy	Shallow submucosa	5-FU and radiation, etoposide	Dead, 22
Our case	SCC	Deep submucosa	CPT-11 and cisplatin	Alive, no recurrence, 55

lar invasion occurred in the deep part of the submucosa, which consisted only of SCC. The vertical margin was positive.

After ESD, he received chemotherapy consisting of CPT-11 (60 mg/m²) on days 1, 8, and 15 plus cisplatin (60 mg/m²) on day 1. However, he

dropped out of chemotherapy during the first course because of grade 3 nausea. Since then, he has desired no therapy. He has been followed-up by CT and EGD. At 55 months after ESD, he is alive and in good condition with no evidence of disease.

DISCUSSION

ECC that are positive for immunohistochemical staining such as chromogranin A, CD56, and synaptophysin are classified as small cell type or large cell type. Approximately 300 cases of small cell type have been described in the literature as small cell carcinoma of the esophagus¹⁾. Similar to small cell carcinoma of the lung, esophageal small cell carcinoma is aggressive. It is found frequently in the advanced stage with lymph node and distant metastasis¹⁾. Standard therapy has not been established. Its prognosis is extremely poor¹⁾.

Four reports have described endoscopic resection (ER) for superficial esophageal ECC including small-cell carcinoma⁴⁻⁷⁾. Takeshita *et al.*⁴⁾ reported endoscopic mucosal resection (EMR) performed for esophageal ECC with invasion depth of the muscularis mucosa. After EMR, this patient received chemotherapy with etoposide and carboplatin. No recurrence was found for 28 months. Three authors⁵⁻⁷⁾ reported cases of esophageal ECC with invasion depth of the submucosa performed by ESD. All three patients suffered lymph node metastasis at 5, 8, and 14 months after ESD. Of them, two died at 22 and 25 months after ESD. Many authors reported that systemic chemotherapy with or without local treatment such as radiotherapy should be regarded as important treatment options for esophageal ECC^{1,8,9)}. Chemotherapy consisting of CPT-11⁸⁾ or etoposide⁹⁾ plus platinum such as cisplatin or carboplatin is effective for esophageal ECC. Such therapy is the standard regimen for small cell carcinoma of the lung. However, all three cases performed by ESD were not treated with chemotherapy consisting of CPT-11 or etoposide plus platinum early after ESD. Apparently, superficial esophageal ECC is extremely aggressive with early systemic relapse after local treatment. These reports suggest that starting chemotherapy as soon as possible after ESD is crucially important for preventing its recurrence.

In our case, the biopsy before treatment failed to yield any diagnosis of ECC. Similarly to our case, three of the four cases in which ER had been conducted failed to reach any diagnosis of ECC before the treatment, which suggests that a diagnosis

of ECC before treatment is difficult. Arima *et al.*³⁾ reported that lesions including the type 4R blood vessel, which does not form an avascular area according to classification of the microvascular pattern, includes a specific histologic type esophageal cancer such as ECC. Ozawa *et al.*⁵⁾ reported one case observed using magnifying endoscopy with NBI as superficial esophageal ECC, which is described as appearing like type 4R. In our case, magnifying endoscopy with NBI revealed no feature of esophageal ECC because many parts of ECC are located in the submucosa, not the mucosa. The value of EUS for the diagnosis of esophageal ECC remains uncertain. In this case, as reported in the literature, if EUS had been conducted before ER, then more accurate diagnosis of invasion depth could have been achieved.

Two mechanisms have been inferred from ECC pathogenesis. Atter *et al.*¹⁰⁾ reported a case which suggested that ECC should be developed by dedifferentiation of SCC in the process of invasion. Ho *et al.*¹¹⁾ reported that a totipotent primitive cell served as the common precursor for squamous cell, adenocarcinoma, and small cell carcinoma of the esophagus. In our case, small-cell, mediate-cell, and large-cell type ECC presented various patterns in the submucosa. The fact that different cells had various patterns, and that SCC bordering ECC showed a lack of lowering of the differentiation level. The clear transition image to ECC suggests that the mechanism of pathogenesis in this case might be that reported by Ho. The histopathological findings of our case are interesting for elucidation of the histogenesis of esophageal ECC.

This report described an extremely rare case of submucosal esophageal ECC combined with SCC resected by ESD. Considering that the patient has remained alive without recurrence for 55 months after ESD, it is also a valuable case for expanding knowledge in this area.

CONFLICT OF INTEREST

The authors declare no conflicts of interest for this article.

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