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【 CASE REPORT 】

Mediastinal Neuroendocrine Carcinoma Slowly Growing for 8 Years after Surgical Resection of Esophageal Squamous Cell Carcinoma

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Abstract:
A 70-year-old woman was referred to our department due to a solitary mediastinal tumor which gradually grew near the site of anastomosis for 8 years after radical surgery of esophageal squamous cell carcinoma. It was difficult to distinguish the lymph node recurrence of esophageal cancer from another tumor of unknown primary origin. Endoscopic ultrasound-guided fine-needle aspiration was performed, and the tumor was diagnosed to be neuroendocrine carcinoma. She received concurrent chemoradiotherapy with etoposide plus cisplatin. After the completion of chemoradiotherapy, the tumor disappeared. A solitary growing tumor which develops after radical resection of cancer would be better to be examined histologically in order to make an accurate diagnosis and select the most appropriate treatment.

Key words: neuroendocrine carcinoma, lymph node, fine-needle aspiration, esophageal squamous cell carcinoma

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Introduction

Neuroendocrine carcinoma (NEC) is a malignant epithelial tumor, and frequent sites of NEC include the digestive tract, lung, and bronchial tube. NEC of unknown primary origin (UPO) is rare and often found in liver or lymph nodes (1). Generally, its prognosis is extremely poor with a rapid increase and early systemic metastases (2, 3). We herein report a case of NEC of UPO which was difficult to distinguish from a recurrence of esophageal squamous carcinoma which had been resected 8 years previously.

Case Report

A 70-year-old woman with an Eastern Cooperative Oncology Group Performance Status of 0 was referred to our department due to mediastinal lymph node swelling although she had no subjective symptoms. Her physical examination was normal. Her serum level of carcinoembryonic antigen was 5.8 ng/mL (normal limit value, <5.0 ng/mL), neuron specific enolase was 14.4 ng/mL (normal limit value, <12.0 ng/mL), and there were no other findings in the laboratory tests. Eight years prior to this presentation, she had undergone lower esophagectomy and total gastrectomy (Roux-en-Y anastomosis) for an esophageal tumor (Fig. 1a). The tumor contained atypical cells which showed sheet-like proliferation in hematoxylin-eosin staining. The atypical cells were accompanied by intercellular bridges (Fig. 1b-d). Based on these findings, it was diagnosed as squamous cell carcinoma, moderately differentiated type. Immunohistochemical staining showed those cells to be partially positive

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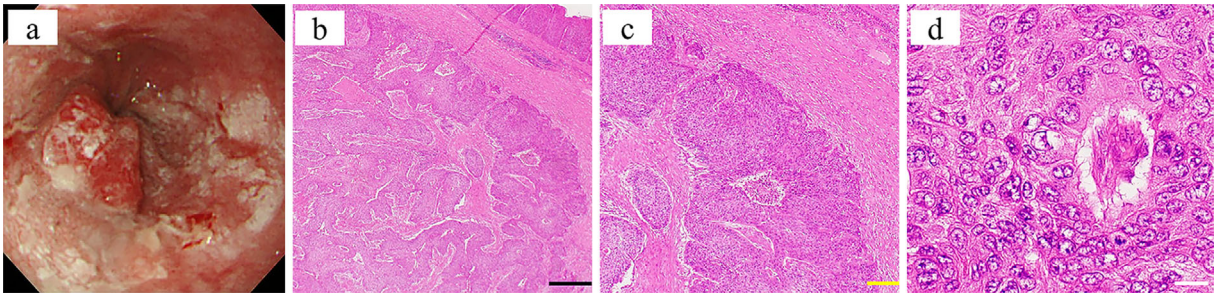

Figure 1. **Eight years prior to this presentation, a type 3 tumor was found in the lower esophagus by esophagoenoscopy (a), and lower esophagectomy and total gastrectomy (Roux-en-Y anastomosis) was performed. The atypical cells showed sheet-like proliferation which were accompanied by intercellular bridges in Hematoxylin and Eosin staining (b-d), and it was diagnosed as moderately differentiated squamous cell carcinoma. The black bar length shows 500 μm, the yellow bar length shows 200 μm, and the white bar length shows 20 μm.**

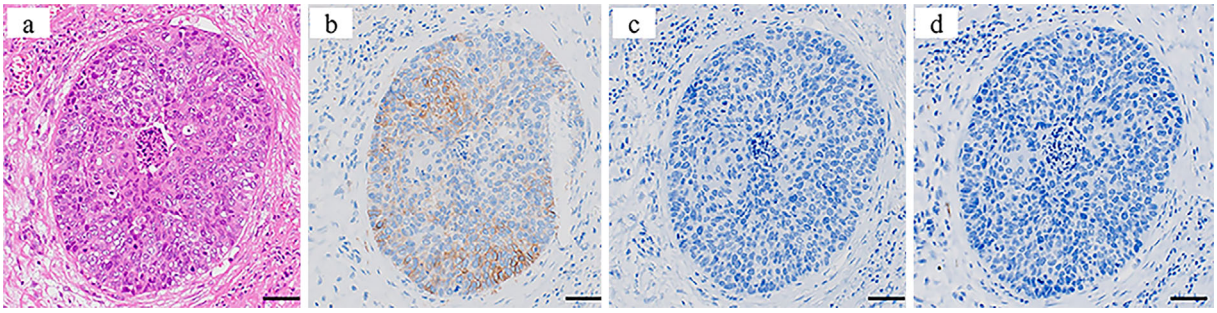

Figure 2. **The tumor cells of previous esophageal squamous cell carcinoma in Hematoxylin and Eosin staining (a) showed that CD56 was partially positive (b), and chromogranin (c) and synaptophysin (d) was negative. The black bar lengths show 50 μm.**

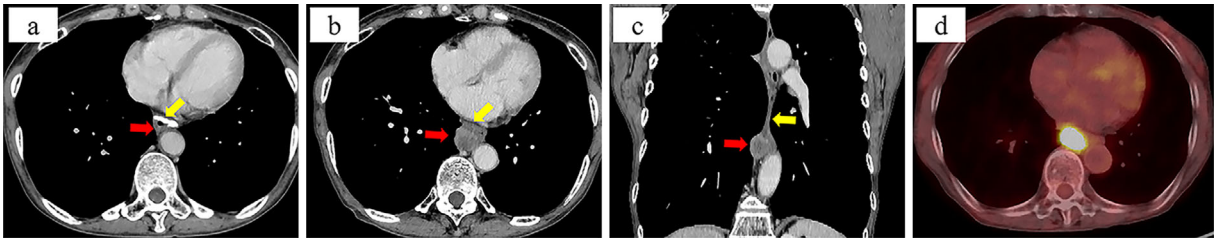

Figure 3. **The initial size of lymph-node swelling was 4 mm in size (a), but it gradually increased to 23 mm over 8 years (b, c). An accumulation of ^{18}F-fluorodeoxyglucose was observed at the same lesion by ^{18}F-fluorodeoxyglucose positron emission tomography-computed tomography (d). Red arrows: tumor, Yellow arrows: esophagus.**

for CD56, and negative for chromogranin A and synaptophysin (Fig. 2). The pathological stage was pT3N1 (station #2), pStage III. As adjuvant chemotherapy, cisplatin plus fluorouracil was administered, but discontinued after only one course because of adverse events such as nausea and anorexia. A small nodule suspected to represent lymph node (station #110) swelling was found by computed tomography (CT) 1 month after the surgery (Fig. 3a). At that time, the lesion was considered to likely be post-operative inflammatory change of the lymph node. However, it gradually increased by a few millimeters every year until reaching 23 mm in size at 8 years after surgery (Fig. 3b, c). An accumulation of ^{18}F-fluorodeoxyglucose (FDG) was observed in the same lesion by FDG positron emission tomography (PET)-CT (Fig. 3d), and no other tumors were detected in whole-body PET-CT. As for this tumor, we could not clinically distinguish whether it was local lymph node recurrence or a new and different tumor.

Esophageal endoscopy revealed a slightly elevated normal mucosa due to the pressure of an extramural mass near the anastomosis (Fig. 4a), and Endoscopic ultrasound (EUS) showed a hypoechoic area with small calcification and a few small cystic components (Fig. 4b). The tumor doppler signal was not rich and we performed EUS-guided fine-needle as-

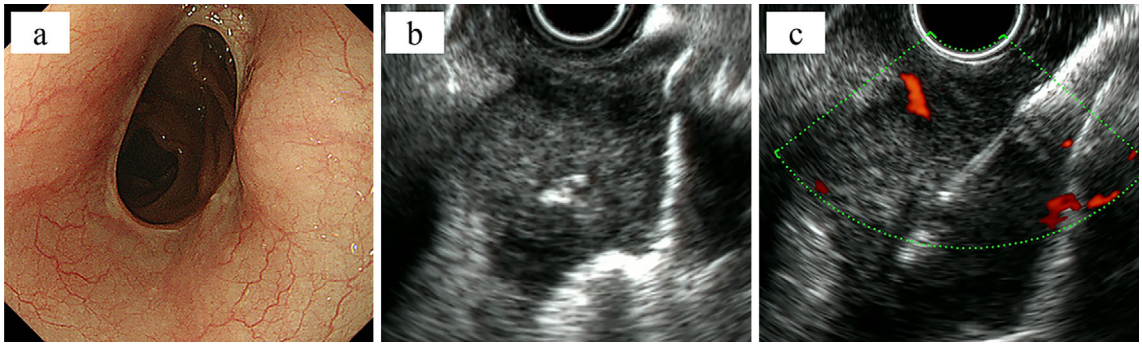

Figure 4. **An extrinsic mass was found above the anastomosis by esophageal endoscopy (a), and the mass showed a hypoechoic area with calcification and cystic components by endoscopic ultrasound (b). Endoscopic ultrasound-guided fine-needle aspiration was performed for the mass in order to obtain a definitive diagnosis (c).**

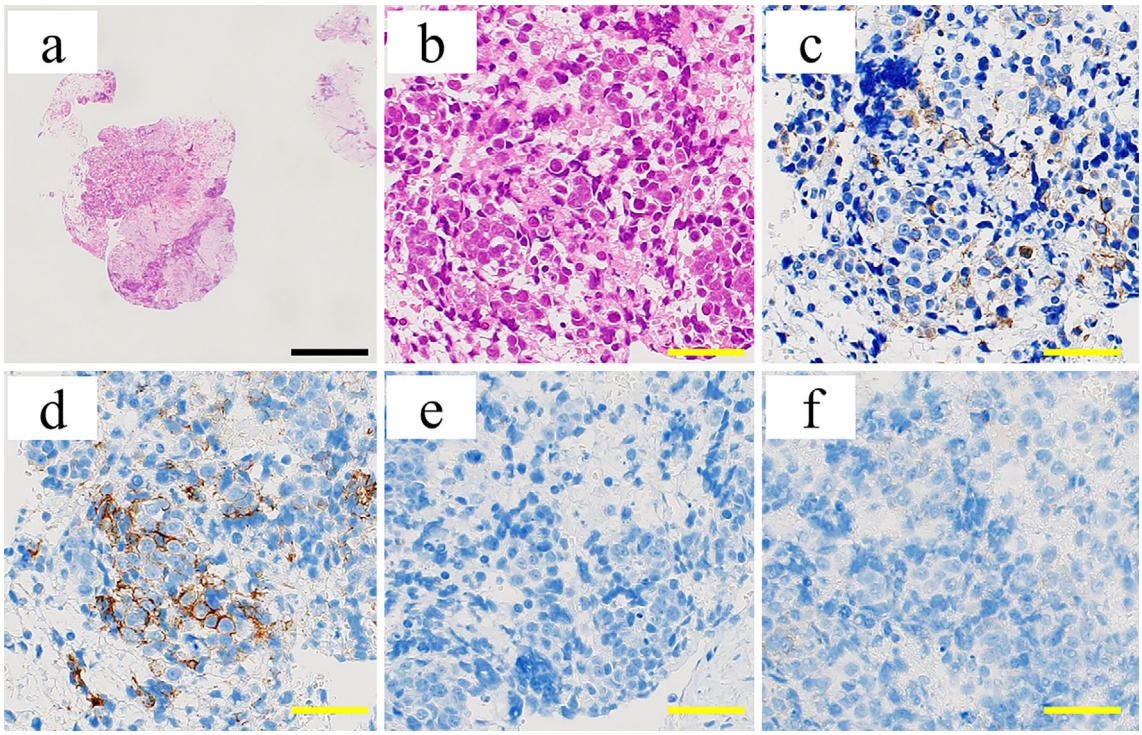

Figure 5. **The specimen showed the histological characteristics of neuroendocrine carcinoma by Hematoxylin and Eosin staining (a, b). The immunostaining showed partially positive for pankeratin (c) and CD56 (d), and negative for chromogranin (e) and synaptophysin (f). The black bar length shows 500 μm and the yellow bar lengths show 50 μm.**

piration (EUS-FNA) of the tumor and inserted a needle of Acquire™ (22 gauge, Boston Scientific, Massachusetts, USA) three times (Fig. 4c). A number of atypical small cells with scarce cytoplasm and multinucleated cells were observed in the obtained specimens (Fig. 5a, b). Those cells were positive for pankeratin and CD56, and negative for chromogranin A and synaptophysin by immunohistochemical staining (Fig. 5c-f). Thus, this tumor was diagnosed as NEC, poorly differentiated type (mitotic counts ≧20 per 10 high-power fields). We explained to the patient and her family that the tumor was strongly suspected to be lymph node metastasis of NEC from UPO, and that surgical treatment was highly invasive and there was little possibility of cure for metastatic NEC. After obtaining informed consent, the patient received etoposide plus cisplatin combination therapy (cisplatin at 80 mg/m^2 on day 1, and etoposide at 100 mg/m^2 on days 1-3, every 3 weeks) and radiation therapy (50 Gy/25 Fr) concurrently. After 4 courses of chemotherapy, the lesion had markedly decreased in size (Fig. 6), and no severe adverse events were observed during chemoradiotherapy. Since then, the tumor has disappeared, and a complete response has now continued for 18 months.

Discussion

Neuroendocrine neoplasms (NEN) are tumors that origi-

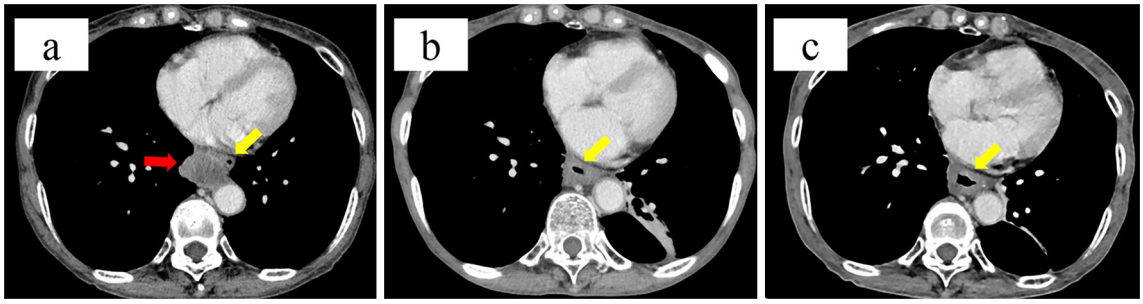

Figure 6. **A computed tomography scan of the tumor images before (a), just after (b), and 18 months after (c) the chemoradiation therapy. The tumor (red arrows) near the esophagus (yellow arrows) has remarkably decreased in size and it has almost completely disappeared.**

Table. **Previous Reports of First-line Chemotherapy for Neuroendocrine Carcinoma.**

Reference Number	Regimen	Primary	N	RR (%)	PFS (month)	OS (month)
13	cisplatin/etoposide	GI, Pancreas, Lung, Unknown primary	18	67	8	19
14	cisplatin/etoposide	GI, Pancreas, Lung, Head and Neck, Unknown primary	41	42	9	15
15	cisplatin/etoposide	Pancreas, Liver, Biliary tract	21	14	1.8	5.8
12	cisplatin or carboplatin/etoposide	GI, Pancreas, Unknown primary	252	31	4	11
16	cisplatin/etoposide	GI, Pancreas, Liver, Biliary tract	46	27	4	7.3
17	cisplatin/irinotecan	Esophagus	12	83	NA	14
18	cisplatin/irinotecan	Stomach	12	75	7	22.6
19	cisplatin/irinotecan	GI, Pancreas	15	7	NA	11.4
20	cisplatin/irinotecan	GI, Pancreas	20	58	4	NA
21	cisplatin/irinotecan	GI, Pancreas	16	57	5.5	10.6
22	cisplatin or carboplatin/irinotecan	Extrapulmonary	25	46	3.7	11.7
16	cisplatin/irinotecan	GI, Pancreas, Liver, Biliary tract	160	50	5.2	13

GI: gastrointestinal tract, RR: response rate, PFS: progression-free survival, OS: overall survival, NA: not available

nate from neuroendocrine cells and are classified into well differentiated NEN (G1, G2 and G3), and poorly differentiated NEN (NEC) based on the mitotic count and/or Ki-67 index, following the 2019 WHO classification (4). No primary origin of NEN is found in approximately 11-22% of patients with NEN, and such cases are designated as NENs of UPO (5). NENs of UPO are often found as multiple liver and lymph node metastases or peritoneal dissemination (1), and have a poorer prognosis compared to metastatic NENs with a known primary site (2, 3).

In this patient, a mediastinal tumor was the only lesion that could be clinically identified. Initially, it seemed to be inflammatory lymph node swelling or a lymph node recurrence of esophageal cancer. If the tumor rapidly grew and multiple lesions appeared, she would have been clinically diagnosed to be a recurrent case of esophageal cancer and then would have been treated with the standard chemotherapy with 5-fluorouracil and cisplatin. However, the tumor had grown very slowly for 8 years after surgery and no other lesions appeared during that time. This was therefore not a typical recurrence of cancer in the lymph nodes. Therefore, we performed EUS-FNA and unexpectedly obtained a definitive diagnosis of NEC. This case taught us that making an appropriate histopathological diagnosis was crucial in patients having a solitary tumor suspected to be metastasis after cancer surgery.

NEC lesions have been reported to often have components of adenocarcinoma and squamous cell carcinoma, and their continuity has been observed histologically (6-8). In addition, neuroendocrine differentiation has been reported in 6% of lung squamous cell carcinomas (9). The operative specimens were dominated by homogeneous squamous cell carcinoma components which were morphologically different from the later diagnosed NEC components. On the other hand, immunostaining of the operative specimens partially showed CD56-positive findings (other neuroendocrine markers were negative); (Fig. 2). Thus, it was considered that there may be a small subgroup which shows differentiation to neuroendocrine cells in the squamous cell carcinoma components. Although this lesion might be generated from stem cells in the lymph node, little has been reported on primary NECs of the lymph nodes (10). Therefore, we considered the mediastinal tumor in this patient to be a lymph node metastatic lesion of NEC, which occurred from esophageal squamous cell carcinoma, although it was not clear when the histological change (undifferentiation) oc-

curred, namely either before or after metastasis. In addition, the reason why the tumor showed such a slow growth in spite of being poorly-differentiated NEC was not clear. For the cancer growth and metastasis, the tumor immune microenvironment is particularly important in addition to constant immune surveillance (11). There might be some immunological defense mechanism against cancer cells in the lymph node, and further study is therefore needed to elucidate this phenomenon.

NEC is similar to small-cell lung cancer in its cell characteristics and clinical manifestations, and chemotherapy based on small-cell lung cancer is recommended in unresectable or metastatic NEC. In the NORDIC study for the NEC of gastrointestinal tract, pancreas, and UPO with unresectable or distant metastasis, the median survival of patients with best supportive care was only 1 month (12). In the patients with chemotherapy including platinum agents, the median survival was 11 months, the response rate was 31%, and the disease control rate was 64%. The combination therapy of etoposide with cisplatin (or carboplatin) and irinotecan with cisplatin showed clinical effects; however, no superiority has been seen between these regimens (12-22); (Table). In addition to systemic chemotherapy, surgery or radiation therapy as a local therapy has been reported to be useful in some patients (23), especially those with localized small-cell lung cancer. In fact, our patient was successfully treated with chemoradiotherapy.

In conclusion, we experienced a unique case of solitary mediastinal tumor that gradually grew for 8 years after surgical resection of esophageal squamous cell carcinoma. EUS-FNA was useful in this case, and led us to make a correct diagnosis and also select the appropriate treatment for NEC of UPO. It is important to make a histological diagnosis in such a difficult cases to differentiate whether such cases are recurrence or not.

The authors state that they have no Conflict of Interest (COI).

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