

Single Case

Esophageal Large-Cell Neuroendocrine Carcinoma with Inconsistent Response to Treatment in the Primary and Metastatic Lesions

Takashi Tomiyama^a Masahiro Orino^a Koh Nakamaru^a
Toshihiro Tanaka^a Ryo Suzuki^a Takashi Okazaki^a Norimasa Fukata^a
Yugo Ando^a Naoyuki Danbara^a Toshiro Fukui^a Chika Miyasaka^b
Kazuichi Okazaki^a

^aDivision of Gastroenterology and Hepatology, Third Department of Internal Medicine, Kansai Medical University, Osaka, Japan; ^bDepartment of Pathology and Laboratory Medicine, Kansai Medical University, Osaka, Japan

Keywords

Esophageal large-cell neuroendocrine carcinoma · Chemotherapy · Esophageal stenosis · Chemoradiotherapy

Abstract

Esophageal large-cell neuroendocrine carcinoma (NEC) is a rare malignant tumor that is characterized by high-grade malignancy and a poor prognosis. However, the rarity of esophageal NEC has prevented the development of an established treatment, and no reports have described a discrepancy in the effectiveness of cisplatin plus irinotecan between primary and metastatic lesions. A 43-year-old Japanese man was referred to our hospital with refractory epigastralgia. A previous gastrointestinal endoscopy had revealed a 50-mm type 2 tumor in the abdominal esophagus. The pathological findings indicated poorly differentiated squamous cell carcinoma. Contrast-enhanced computed tomography revealed a metastatic liver tumor.

One cycle of fluorouracil and cisplatin was not effective, and endoscopy was repeatedly performed. The pathological findings indicated a large-cell malignant tumor with tumor cells that were positive for CD56, synaptophysin, and Ki-67 (>80%). Based on a diagnosis of esophageal large-cell NEC with a metastatic liver tumor, the patient received cisplatin plus irinotecan bi-weekly. After 4 months, computed tomography revealed marked shrinkage of the metastatic tumor, but the patient complained of dysphagia. Endoscopy revealed enlargement of the primary tumor, which was then treated using radiotherapy plus fluorouracil and cisplatin. The primary tumor subsequently shrank, and the patient's symptoms were relieved, but the metastatic tumor grew. Thus, chemoradiotherapy could be an option for managing a primary esophageal large-cell NEC that does not respond to chemotherapy alone. However, the possibility of an inconsistent response to therapy in primary and metastatic lesions should be considered.

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Background

Esophageal neuroendocrine carcinoma (NEC) is a rare malignant neoplasm that is characterized by a high malignant potential, rapid growth, and a poor prognosis [1]. However, the rarity of NEC has impeded the development of a standard chemotherapy regimen. Based on the clinical and histopathological similarity between NEC and small cell lung cancer (SCLC), the chemotherapeutic regimens for gastrointestinal NEC are generally the same as those for extensive SCLC, with one widely used option being etoposide (VP-16) plus cisplatin (CDDP) [2–5]. Nevertheless, evidence from the Japan Clinical Oncology Group study (JCOG9511) revealed that administering irinotecan (CPT-11) plus CDDP provides a better prognosis among patients with SCLC than does VP-16 plus CDDP [6]. Considering the similarity between NEC and SCLC, Japanese patients with metastatic esophageal NEC are commonly treated using CPT-11 plus CDDP [7, 8].

We report our experience with a case of esophageal large-cell NEC that had a unique chemotherapeutic response, as the metastatic and primary tumors responded differently to CPT-11 plus CDDP. The primary tumor responded to later concurrent radiotherapy and chemotherapy using 5-fluorouracil (5-FU) plus CDDP, although the metastatic tumor subsequently grew.

Case Report

A 43-year-old Japanese man had had a 2-month history of epigastralgia and abdominal fullness and had been diagnosed with stage IV esophageal cancer before being referred to our center for chemotherapy. A previous gastrointestinal endoscopy had revealed a 50-mm type 2 tumor in the abdominal esophagus, located 45 cm from the incisors. The pathological findings from the biopsy specimens revealed poorly differentiated squamous cell carcinoma. Contrast-enhanced computed tomography (CT) also revealed a 90-mm metastatic liver tumor in the right lobe. The patient did not have a history of esophageal cancer or any related risk factors (e.g., alcohol consumption or smoking) and was not receiving any medication.

A physical examination revealed severe hepatomegaly with tenderness. Laboratory findings revealed a white blood cell count of 5,000/ μ L and a C-reactive protein level of 8.0 mg/dL, but the level of squamous cell carcinoma antigen was not elevated. An initial cycle of 5-FU plus CDDP did not improve his symptoms or the laboratory findings. Repeated endoscopy revealed

that the type 2 tumor at the abdominal esophagus had not changed (Fig. 1a). Hematoxylin and eosin staining of the second biopsy specimen revealed invasive large cells with significant cytoplasm, prominent nuclei, and vesicular chromatin (Fig. 1b). Immunohistochemical staining revealed that the tumor cells were positive for CD56 and synaptophysin (Fig. 1c, d), and that >80% of the tumor cells were positive for Ki-67 (Fig. 1e). Contrast-enhanced abdominal CT revealed that the metastatic liver tumor had grown to a diameter of 120 mm (Fig. 1f). The serum neuron-specific enolase level was 109.5 ng/mL (normal range: 0–15). Thus, the final diagnosis was metastatic large-cell NEC of the esophagus (grade 3).

The patient subsequently received chemotherapy using intravenous infusions of CTP-11 (60 mg/m²) plus CDDP (30 mg/m²) every other week. After 9 cycles over 4 months, his epigastralgia and abdominal fullness were relieved. CT revealed a marked reduction in the size of the metastatic liver tumor (from 120 to 75 mm in diameter; Fig. 2a). No severe adverse effects were observed during this round of treatment, although the patient complained of newly developed dysphagia, and repeat endoscopy revealed clear enlargement of the primary tumor (Fig. 2b). Thus, the patient received chemotherapy using concurrent CDDP and 5-FU (CDDP: 70 mg/m² on days 1 and 29; 5-FU: 700 mg/m² in continuous infusions on days 1–5 and 29–33) along with radiotherapy (60 Gy in 2-Gy doses, 5 days per week). Repeat endoscopy 1 month after completing this course of chemoradiotherapy revealed a dramatically smaller esophageal tumor (Fig. 3a), but an enlarged metastatic tumor (Fig. 3b).

The patient subsequently received biweekly treatment with CPT-11 plus CDDP to reduce the size of the liver tumor, but the additional 6 cycles of this treatment led to a chemotherapy-refractory status, with no response observed in the metastatic liver tumor. In addition, the metastatic tumor did not respond to subsequent weekly paclitaxel treatment. The patient ultimately died of liver failure 11 months after starting treatment.

Discussion

NEC is pathologically classified into small-cell and large-cell types. Primary esophageal large-cell NEC is very rare [2, 9], with no established treatment for it. However, with the similarity in the clinical course and histopathological features of NEC and SCLC, inoperable NEC is generally treated using the same chemotherapy regimen as for SCLC, regardless of whether it is of the small-cell or the large-cell type. Even in operable cases, adjuvant chemotherapy is part of the treatment, as it may provide a better prognosis than surgery alone [1, 10]. CDDP is a critical cytotoxic agent and is usually combined with VP-16 or CPT-11 as the first line of treatment. Thus far, second-line and later treatments for esophageal NEC have remained poorly defined. Radiation therapy is another therapeutic option, although experience with this approach is limited [11].

The present case involved a unique clinical course, as the response of the metastatic tumor to treatment with CDDP plus CPT-11 was the opposite of the response observed in the primary tumor; the primary tumor responded to radiation therapy plus 5-FU and CDDP. This clinical course suggests that radiation therapy plus 5-FU and CDDP was able to control the primary esophageal tumor but not the metastatic liver tumor, making it difficult to reach an optimal solution to control both primary and metastatic lesions. Dysphagia due to growth of the primary tumor reduces the quality of life extremely, specifically in the later stages of the disease. Esophageal stenting is a palliative option for dysphagia. Although recent esophageal stents possess an antireflux technology, stenting of distal esophageal stenosis increases the risk of gastroesophageal reflux and aspiration, as the stent should pass the gastroesophageal

junction [12]. In our patient, we opted for chemoradiotherapy to alleviate the dysphagia, resolving the issue in the patient. Nonetheless, the chemotherapeutic regimen of 5-FU plus CDDP and radiotherapy failed to control the growth of the metastatic lesion, indicating that though this combination might have been a good choice for controlling the primary lesion, it was not the optimal regimen to stop the growth of the metastatic lesion. Thus, although the combination of radiotherapy and CPT-11 increases the risk of radiation pneumonitis [13], concurrent radiotherapy and chemotherapy with CDDP and CPT-11 may be a better choice in managing both primary and metastatic esophageal NEC.

Statement of Ethics

Informed consent was not obtained because the patient cannot be identified based on the presented data.

Disclosure Statement

None of the authors have any conflict of interest to disclose.

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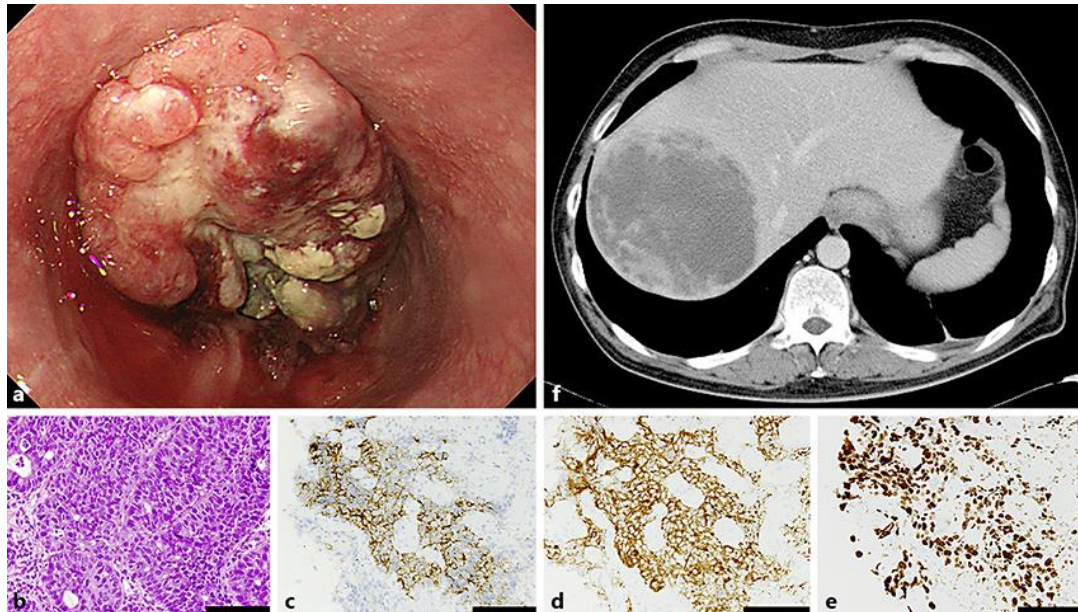


Fig. 1. Clinical findings prior to cisplatin plus irinotecan treatment after 1 cycle of fluorouracil plus cisplatin chemotherapy. **a** The endoscopic findings revealed a 50-mm semicircular invasive ulcerative tumor in the abdominal esophagus. **b** Hematoxylin and eosin staining of the biopsy specimen revealed a large-cell neoplasm. Immunohistochemistry testing for CD56 (**c**), synaptophysin (**d**), and Ki-67 (**e**) revealed that the tumor was a neuroendocrine carcinoma (grade 3). We certified antibody accuracy using tissue microarray specimens, and compared the staining magnitude between our specimens and the known TMA samples. Scale bars, 100 μ m. **f** Contrast-enhanced computed tomography revealed a metastatic tumor with a diameter of 120 mm in the right lobe of the liver which enlarged after 1 cycle of fluorouracil plus cisplatin chemotherapy.

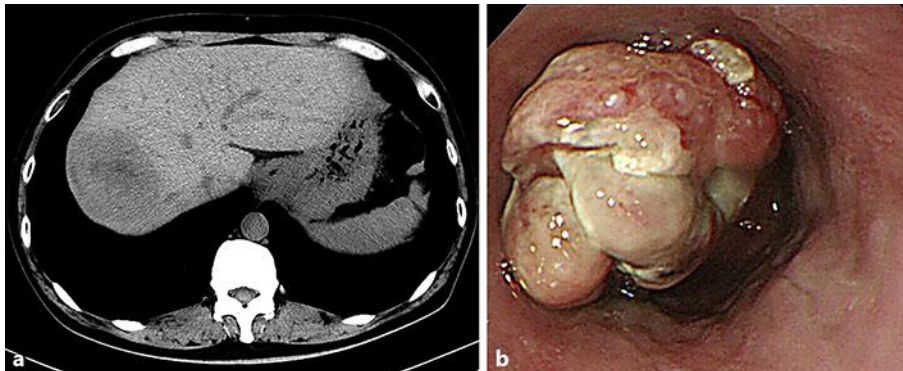


Fig. 2. Findings after 9 cycles of cisplatin plus irinotecan chemotherapy. **a** Computed tomography revealed marked shrinkage of the metastatic liver tumor (from 120 to 75 mm in diameter). **b** Repeat endoscopy revealed an enlarged primary tumor.

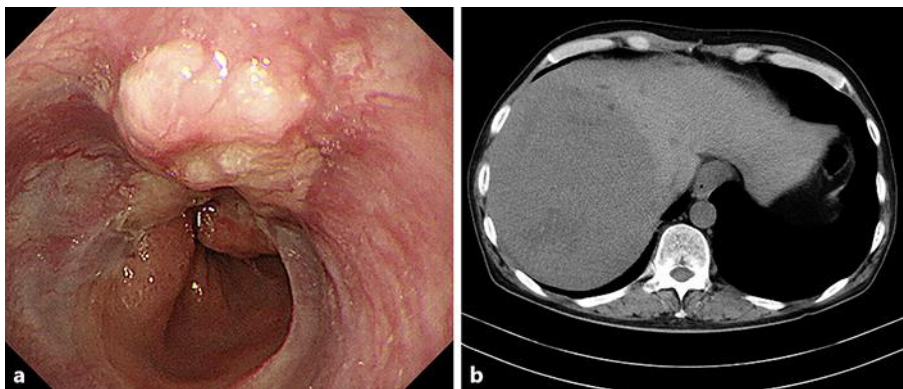


Fig. 3. Findings after radiotherapy plus fluorouracil and cisplatin chemotherapy. **a** Repeat endoscopy revealed marked shrinkage of the primary tumor. **b** Computed tomography revealed an enlarged metastatic tumor (from 75 mm after the first series of chemotherapy to 120 mm in diameter).