

## Conversion to Neuroendocrine Carcinoma from Squamous Cell Carcinoma of the Esophagus After Definitive Chemoradiotherapy

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**Abstract.** *Background/Aim:* Neuroendocrine carcinoma (NEC) of the esophagus is rare and aggressive. We herein report a case of a patient who showed NEC conversion from squamous cell carcinoma (SCC) of the esophagus in the recurrent lesion after definitive chemoradiotherapy. *Case Report:* The patient was a 57-year-old Japanese male with mid-thoracic esophageal carcinoma diagnosed as SCC with invasion of the submucosal layer. After definitive chemoradiotherapy, the esophageal tumor completely disappeared. Two months later, local recurrence was recognized at the same location and salvage surgery was performed. An immunohistochemical examination of the resected specimen revealed that most of the recurrent tumor had neuroendocrine (NE) differentiation, although a retrospective review of the initial biopsy specimen showed no involvement of NE differentiation. *Conclusion:* This case is significant not only in bringing attention to the possibility of NEC conversion from SCC after chemoradiotherapy, but also in discussing tumors originating in the esophagus.

Surgical resection has been the gold standard of treatment for localized squamous cell carcinoma (SCC) of the esophagus. However, this carcinoma is fairly sensitive to radiation, as well as to chemotherapeutic agents, such as cisplatin and 5-fluorouracil (5-FU). Definitive chemoradiotherapy (CRT) is,

therefore, generally applied for far-advanced esophageal squamous cell carcinomas (ESCC) and has recently been adopted even for resectable SCC of the esophagus, with satisfactory results reported regarding patients' prognosis, as well as local control rate. However, the increasing use of definitive CRT has resulted in the need to treat the residual lesions or recurrent tumors that appear after treatment. Salvage esophagectomy has been indicated for such lesions, although the surgical risk is still considered extremely high with high mortality and morbidity rates (1).

Neuroendocrine carcinoma (NEC) of the esophagus is a rare histological entity. In the past, NEC was referred to as small cell carcinoma; however, in recent years, it has been referred to as carcinoma with neuroendocrine (NE) differentiation (2). Huang *et al.* (3) reviewed the incidence of esophageal NEC, which accounts for 0.5%-5.9% of esophageal cancer cases in China, 0.8%-2.8% in Japan and 1%-2.8% in Westerners. NEC of the esophagus is thought to be highly malignant and to have a poor prognosis (4-6). Histologically, this type of tumor frequently exhibits small SCC differentiation (3). However, NE differentiation has been observed in cases with basaloid squamous carcinoma (BSCC), as well as those with adenocarcinoma (7, 8).

We herein report a case of a patient who underwent salvage esophagectomy for recurrent esophageal cancer histologically diagnosed as superficial SCC with biopsy specimen before definitive CRT. The histological examination of the resected specimen revealed that most of the submucosal tumor consisted of neuroendocrine cells.

### Case Report

The patient was an asymptomatic 57-year-old Japanese male. He had a pack-a-day history of tobacco use and consuming three glasses of white liquor (*shochu*) per day for 35 years.

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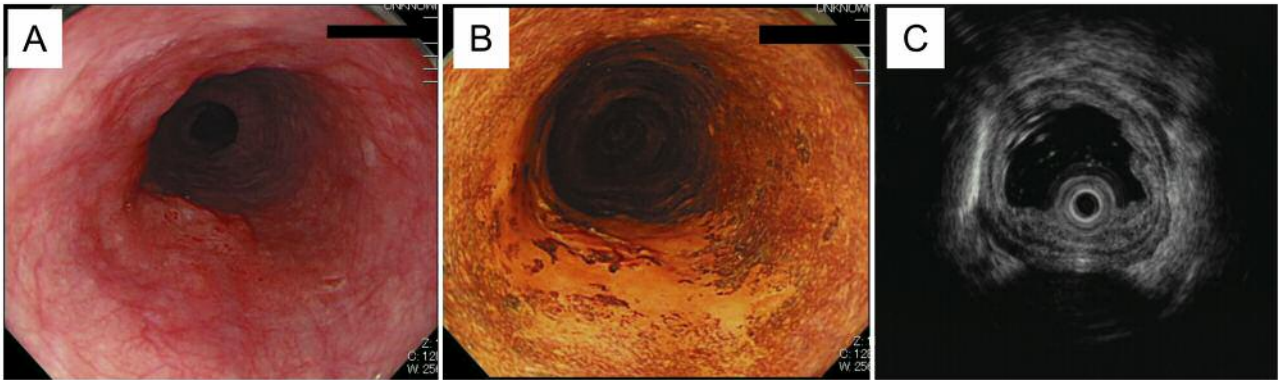


Figure 1. The endoscopic and ultrasonographic findings before treatment. A. Esophageal endoscopy revealed irregularity of the mucosa of the mid-thoracic esophagus 30 cm from the dental arch. B. The lesion was visualized as a Lugol-voiding lesion. C. Ultrasonography revealed the depth of invasion to be up to the submucosal layer.

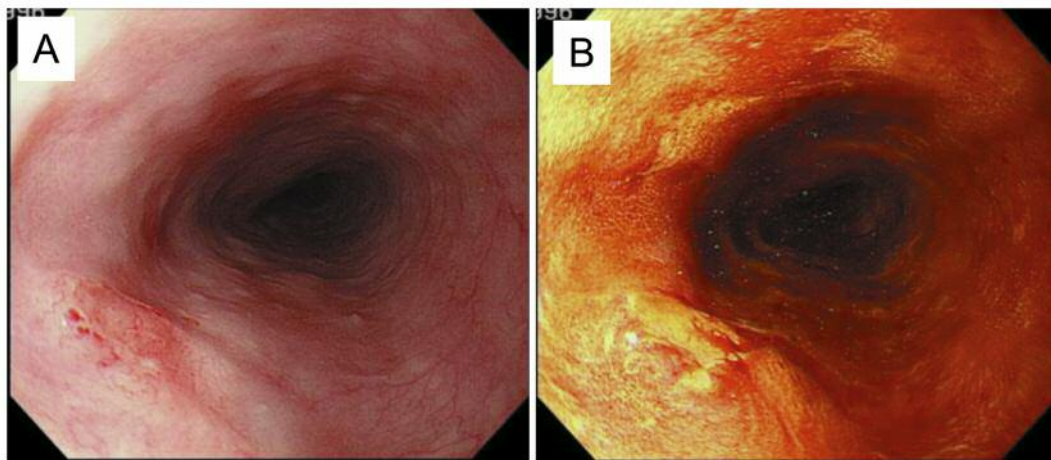


Figure 2. Endoscopy performed 2 months after completion of definitive chemoradiotherapy. A. A slightly elevated lesion was visualized in a similar location to the initial tumor. B. Endoscopy with Lugol staining revealed that part of the elevated lesion was covered with normal epithelium; however, there were unstained areas in the lesion as well.

However, he had no noteworthy particular medical history. An upper gastrointestinal fibroscopy, performed during a routine annual medical check, revealed irregularity of the mucosa in the mid-thoracic esophagus, 30 cm from the dental arch (Figure 1). The histological diagnosis using a biopsy specimen was moderately differentiated SCC. Both esophagoscopy and esophagography revealed the depth of the invasion to be submucosal. Computed tomography revealed neither node metastasis nor distant metastasis (T1N0M0, Stage IA). The patient wished to receive definitive CRT as an initial treatment. A total of 60 Gy of radiation plus 2 cycles of FP therapy (cisplatin 70 mg/m<sup>2</sup> on Day 1 and 5-FU 700 mg/m<sup>2</sup> on Days 1-5 for 1 cycle) were performed. After definitive CRT was completed, the

esophageal tumor completely disappeared and no viable cancer cells were recognized in the biopsy specimen.

Endoscopy, performed two months after the completion of the definitive CRT, revealed a slightly elevated lesion in a similar location to the initial tumor (Figure 2). The lesion proved to be a carcinomatous lesion, suggesting local recurrence. Salvage esophagectomy and reconstruction with a gastric tube was performed. A histological examination of the resected specimen revealed that most of the tumor comprised round-shaped carcinoma cells with a high nucleus-to-cytoplasm ratio in a nested pattern invading the submucosa and accompanied by a small area of squamous cell carcinoma with intraductal spread (Figure 3). Immunohistochemically, the round-shaped carcinoma cells

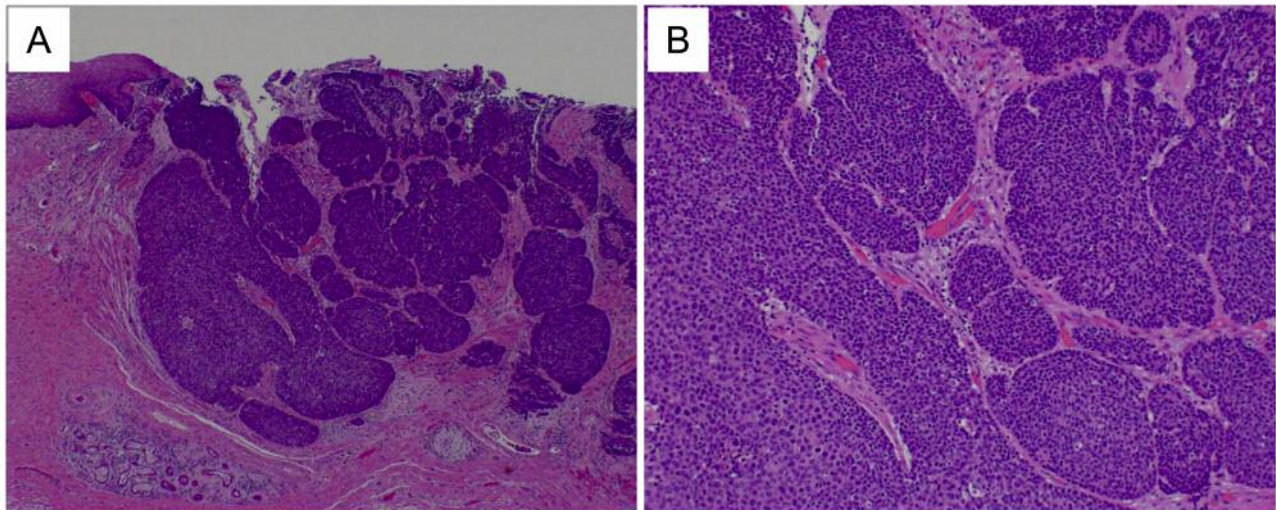


Figure 3. Microscopic findings of resected specimen. The section shows an area of proliferation of round-shaped carcinoma cells with a high nuclear/cytoplasmic ratio in a nested pattern, invading the submucosa. (H.E. (a) 40 $\times$ , (b) 100 $\times$ )

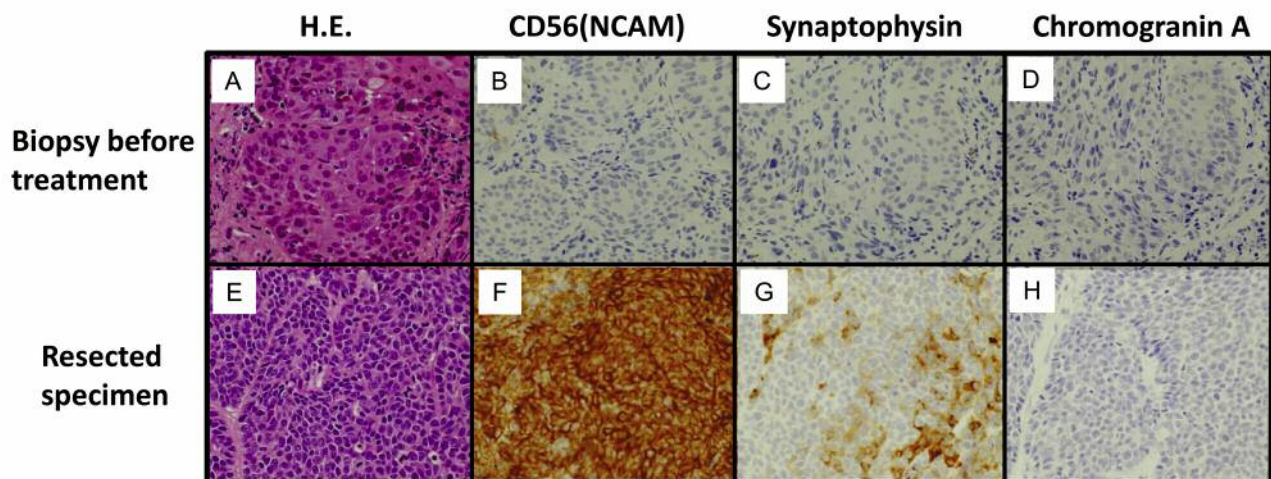


Figure 4. H.E. and immunohistochemical staining of the biopsy specimen before treatment (A-D) and of the resected specimen (E-H). The biopsy specimen immunohistochemically had no staining for CD56 (NCAM), synaptophysin or chromogranin A. In the resected specimen, the round-shaped carcinoma cells were diffusely positive for CD56 (NCAM), focally positive for synaptophysin and negative for chromogranin A.

were diffusely positive for CAM5.2 and CD56 (NCAM), focally positive for synaptophysin and CK903 and negative for chromogranin A (Figure 4). The Ki-67 index was 30%. Taken together, these features indicate squamous cell carcinoma with predominant NE features (NEC). Neither vascular invasion nor node metastasis were observed.

Four courses of adjuvant chemotherapy with carboplatin (AUC5, Day 1) and etoposide (80 mg/m<sup>2</sup>, Days 1-3) were performed. The patient is alive without any recurrence two years after salvage esophagectomy.

## Discussion

NEC is a poorly differentiated, high-grade malignant neoplasm comprising small- or large-to-intermediate cells with marked nuclear atypia, multifocal necrosis and a high number of mitoses (>20 per 10 high-power fields). Immunohistochemistry findings for chromogranin A, synaptophysin, CD56 and neuron-specific enolase (NSE) are usually positive with this neoplasm. Among these markers, synaptophysin is the most sensitive (2) and the KI-67 index



is >20% (6). Both histological and immunohistochemical findings of the resected specimen in the present case were compatible with NEC.

NEC of the esophagus is frequently associated with squamous cell carcinoma components: Serial histological examination of 42 primary high-grade NEC specimens of the esophagus revealed the involvement of squamous cell carcinoma *in situ* in 50% of cases (3). In the current case, a small portion of SCC was also associated in the NEC component. BSCC, a variant of squamous cell carcinoma, frequently contains multiphasic carcinomas, including SCC and NE differentiation, and is thought to be a distinct neoplasm with multi-potential differentiation (7). Our present findings support the concept described by Vos *et al.* (9) that NEC is endodermal in origin and derives from pluripotent cells of basal, squamous and glandular elements of the same lesion.

Several authors have reported the significance of NE differentiation in resistance to chemoradiotherapy in patients with adenocarcinoma. Shia *et al.* (10) examined the NE component in rectal adenocarcinoma before and after radiotherapy with and without chemotherapy. They reported an increased frequency and density of cells with an endocrine phenotype in adenocarcinomas of the rectum that had been irradiated, noting that the extent of endocrine differentiation was proportional to the degree of treatment response. Wang *et al.* (8) emphasized the significance of NE differentiation in adenocarcinoma of the esophagus and esophagogastric junction after CRT. The proportion of tumor cells with NE differentiation increased from 6% in the pretreatment biopsy specimens to 47% in the post-irradiated resected specimens. Furthermore, the prognosis was significantly worse in patients who had residual tumors with NE differentiation than in those without NE differentiation. These results suggested that tumor cells with NE differentiation were more resistant to neoadjuvant (chemo-) radiotherapy in patients with adenocarcinoma of the esophagus or rectum. Two main hypotheses as to why NE differentiation increases after chemoradiotherapy were presented: First, tumor cells with NE differentiation may be more resistant to the cytotoxic insult caused by neoadjuvant therapy; Second, cytotoxic injury may induce NE differentiation in tumor cells (8, 10). The present case is the first instance of esophageal cancer with NEC conversion from SCC after chemoradiotherapy.

In this study, retrospective immunohistochemical staining in the initial biopsy specimen after the histological examination of the resected specimen revealed that NE differentiation was predominant. The biopsy specimen revealed no staining for CD56 (NCAM), synaptophysin or chromogranin A (Figure 4). These results indicate that NE differentiation was not observed in the biopsy specimen before the treatment. Cellular heterogeneity might have

existed in the tumor before the treatment and the NE-differentiated cells, which had not been able to be detected due to their small number, might have then multiplied, being resistant to CRT. Another possibility is that NE differentiation might have occurred from multi-potential cells within the initial SCC.

No chemotherapeutic regimens effective for NEC of the esophagus have so far been established as esophageal NEC is aggressive, with prognosis being generally extremely poor. We, therefore, performed adjuvant chemotherapy against NEC (small-cell carcinoma) of the lung. The current rare case is considered to be very significant not only from a clinical perspective, bringing attention to the possibility of NEC conversion from SCC after CRT, but also in fostering discussion of tumors originating in the esophagus.

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