

Small Cell Type of Esophageal Neuroendocrine Carcinoma Resembling a Submucosal Tumor

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(Received March 17, 2015; Accepted April 7, 2015)

We report a rare case of primary small cell type esophageal neuroendocrine carcinoma with a unusual endoscopic form similar to a submucosal tumor with the results of the histological and immunohistochemical analyses. A 57-year-old woman with dysphagia was referred to our hospital for further examination and treatment, and was diagnosed as type 1s esophageal carcinoma in the middle thoracic esophagus. Endoscopy revealed a protruding esophageal carcinoma resembling a submucosal tumor with an irregular and nodular surface covered by non-neoplastic epithelium stained with iodine. Analysis of the esophageal biopsy specimen revealed poorly differentiated squamous cell carcinoma. Based on a diagnosis of type 1s carcinoma in the middle thoracic esophagus that was 5 cm in size longitudinally, a radical esophagectomy with three-field lymph node dissection was performed. The pathological examination with histological and immunohistochemical analysis of the resected specimen revealed a small cell type neuroendocrine carcinoma overlaid by a non-neoplastic epithelium, extending into the adventitia without lymph node metastasis (T3, N0, M0, Stage II). However, multiple metastases in the brain and lung developed 3 months postoperatively, and the patient died of the cancer 7 months after the operation. This was a rare case of a highly malignant primary small cell type esophageal neuroendocrine carcinoma showing extremely rare form.

Key words: esophageal carcinoma, neuroendocrine carcinoma, small cell carcinoma

INTRODUCTION

Squamous cell carcinoma is the most common malignant neoplasm of the human esophagus. Neuroendocrine carcinoma frequently arises in the bronchial tree, but is very rare in the gastrointestinal tract, and it rarely occurs in the esophagus as small cell carcinoma [1]. Its prognosis is poor because of its aggressive nature and the high incidence of distant metastasis to the liver, lung, bone, and brain. However, no standard treatment for small cell type neuroendocrine carcinoma of the esophagus has been established. Here, we present a case of a highly malignant primary small cell type esophageal neuroendocrine carcinoma, which is a rare endoscopic form resembling a submucosal tumor, with histological and immunohistochemical analyses.

CASE REPORT

A 59-year-old woman who had been suffering from dysphagia for 2 months underwent endoscopic examination in another hospital, which revealed a 5-cm protruding lesion in the thoracic esophagus. The patient referred to Tokai University Hospital for further examination and treatment. She was a non-smoker and not

a habitual drinker. The general physical examination at admission did not reveal any abnormalities. All laboratory data were within the normal ranges except for slight anemia, and squamous cell carcinoma antigen and carcinoembryonic antigen levels, which were 0.6 ng/ml and 0.7 ng/ml, respectively.

Double contrast esophagography demonstrated a protruding lesion with a slight barium fleck. The tumor was 5-cm in size longitudinally, and had an irregular and nodular surface. It was located on the left-posterior wall of the middle thoracic esophagus (Fig. 1). Esophagoscopy revealed a protruding tumor, again with an irregular and nodular surface, that was covered by non-neoplastic esophageal epithelium as revealed by iodine staining, resembling a submucosal tumor by conventional and chromoendoscopic examination (Fig. 2A, B). Pathological examination of the preoperative biopsy material revealed poorly differentiated squamous cell carcinoma. Thoracic and abdominal computed tomography showed no evidence of metastasis.

The preoperative diagnosis was type 1s esophageal carcinoma invading proper muscle (T2) without lymph node and distant organ metastasis [2]. A standard radical subtotal esophagectomy with three-field lymph



Fig. 1 Double contrast esophagography revealed a protruding lesion with a nodular change and slight barium fleck. The tumor was 5-cm in size longitudinally, and the tumor was located on the left-posterior wall of the middle thoracic esophagus.

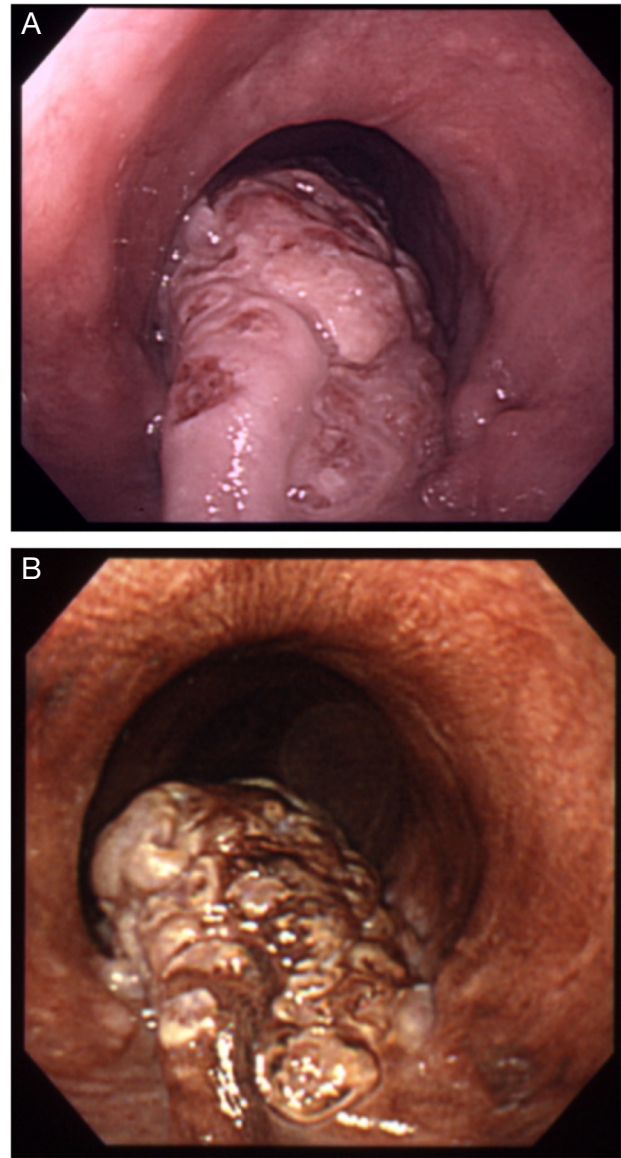


Fig. 2 Endoscopic findings.
A: Conventional endoscopic examination revealed an unusual submucosal tumor-like type 1s lesion with nodular surface and central slight depression covered with non-neoplastic epithelium at 28–33cm distant from the incisor.
B: Chromoendoscopic examination revealed type 1s tumor stained with iodine.

node dissection and cervical esophagostomy using a thoraco-laparotomy was performed. The patient was discharged 3 weeks postoperatively without any complications. The patient refused postoperative adjuvant chemotherapy. She became to complain of headache and nausea 3 months after the operation, when multiple metastases in the brain and lung were detected by computed tomography. Whole skull irradiation and therapeutic chemotherapy with cisplatin and 5-fluorouracil were performed, but she died of the cancer 7 months after the operation.

PATHOLOGICAL FINDINGS

Gross Findings of the Resected Tissue Specimens

The protruding lesion measured 45 × 30 × 20 mm in size, and occupied approximately half of the

circumference of the esophageal lumen. The tumor showed expansive growth and irregular and nodular lobulation with a small ulcerative part at the top of the tumor. Most of the surface of the tumor was covered with non-neoplastic squamous epithelium and resembled a submucosal tumor macroscopically.

Microscopic Findings of the Resected Specimen

The protruding tumor showed invasive proliferation of cancer cells, and was predominantly composed of solid tumor nests in a lobular configuration. The solid tumor nests were sharply demarcated by surrounding fibrous stroma and invaded into the adventitia of the esophageal wall with some vascular and lymphatic permeation. The carcinoma cells had round, hyperchromatic, and occasionally large and vesicular nuclei

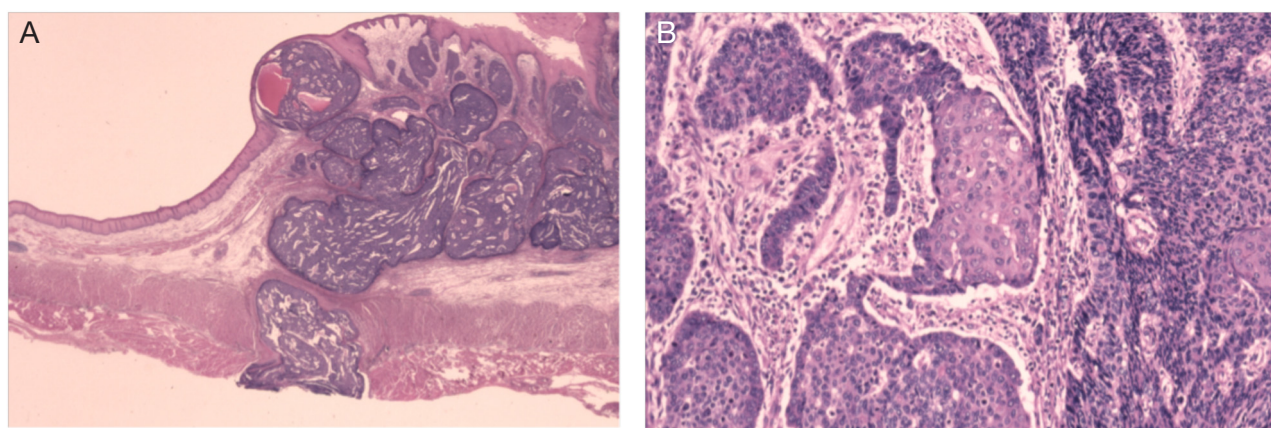


Fig. 3 Microscopic findings of the resected specimen.
A: Microscopic findings of the resected specimen were characteristic of predominantly subepithelial expansive growth pattern (original magnification x2, H & E).
B: Magnified findings of small cell carcinoma showed combined type with squamous cell carcinoma components (original magnification x35, H & E).

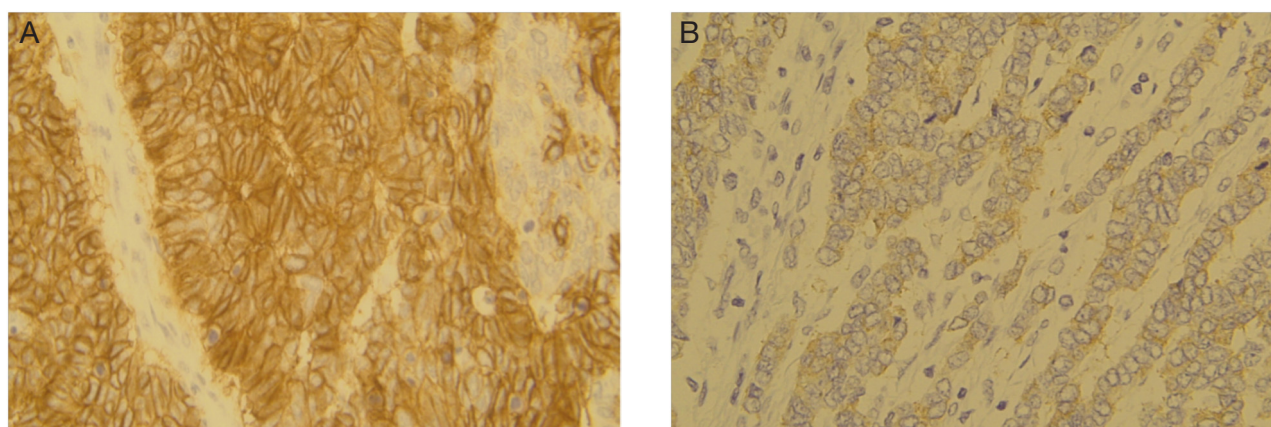


Fig. 4 Immunohistochemical findings.
A: Neural cell adhesion molecule (NCAM; CD56) immunoreactivity is observed in the small cell carcinoma component (original magnification x200).
B: Synaptophysin immunoreactivity is observed in the small cell carcinoma component (original magnification x200).

with scant cytoplasm and a high nuclear-to-cytoplasmic ratio. Focal, comed-like central necrosis was focally present in the tumor nests, which also had a palisading appearance with rosette formation at their periphery. Tiny components of the squamous cell carcinoma were sporadically detected, while the majority of the invasive carcinoma was composed of small cell type neuroendocrine carcinoma (Fig. 3A, B).

Immunohistochemistry

The carcinoma cells were stained positive for neural cell adhesion molecule (NCAM; CD56), synaptophysin, cytokeratin 20 (CK20), CK-CAM5.2, and bcl-2, and negative for chromogranin-A, neuron specific enolase (NSE), protein gene peptide 9.5 (PGP 9.5) and S-100 (Fig. 4A, B).

On the basis of the microscopic and immunohistochemical findings, the esophageal lesion was classified as small cell type neuroendocrine carcinoma combined with squamous cell carcinoma, extending into the adventitia without metastasis in 71 dissected lymph nodes. The infiltrating pattern was expansive (INF-a) and some lymphatic and blood vessel invasion were noted (ly1, v1). According to the Japanese guidelines

for clinical and pathologic studies on carcinoma of the esophagus, the pathological stage was classified as Stage II (T3, N0, M0) [2].

DISCUSSION

Squamous cell carcinoma is the most common malignant neoplasm of the esophagus in Japan. Small cell type neuroendocrine carcinoma of the esophagus is a rare tumor, accounting for about 1% of all esophageal malignancies, but this tumor is usually found in esophagus in the gastrointestinal tract [1-4]. McKeown described the first case of primary undifferentiated small cell carcinoma of the esophagus in 1952 [5], and the first report from Japan was by Taniguchi *et al.* in 1973 [6].

Although several treatment modalities have been described employing chemotherapy, radiation, and surgical resection in combination, none is considered to be very effective in this tumor type. No standard treatment has been established yet, and the treatment strategy is often indicated based on that used for lung cancer [7]. Limited disease, defined as a tumor confined to the esophagus and local regional nodes within its radiation field, is usually treated using chemo-radiation therapy [7]. Endoscopic diagnosis of the

tumor at an early stage is very important, although in some cases this may be missed using endoscopy or endoscopic biopsy. The majority of cases are thus diagnosed in the late stage of the disease at presentation. The exact biopsy of the tumor is occasionally difficult because the tumor surface is covered with non-neoplastic epithelium. In this case, the protruding lesion showed irregular and nodular lobulation covered with non-neoplastic squamous epithelium, and was a rare endoscopic form similar to a submucosal tumor. The biopsy specimen may not contain small cell carcinoma components, due to its subepithelial growth pattern. Discrepancies between the endoscopic and histopathological diagnosis need to be jointly reviewed by clinicians and pathologists. In cases where small cell type neuroendocrine carcinoma of the esophagus is diagnosed based on the biopsy, a non-surgical treatment, such as chemo-radiation therapy, is generally selected due to its malignant nature and very poor prognosis. In the case we report here, primary small cell type neuroendocrine carcinoma of the esophagus was not diagnosed from the biopsy of the preoperative endoscopic examination, and we therefore performed radical surgery as an initial treatment. Unfortunately, the patient also refused to undergo postoperative adjuvant chemotherapy.

Subsequent papers have reported an occasional invasive or in situ squamous cell component of esophageal neuroendocrine carcinoma [4, 8–10]. Small cell type neuroendocrine cell carcinoma of the esophagus is subdivided histopathologically into a pure type and a combined type in which squamous cell carcinoma is also present, but the significance of these sub-classifications has not been established [10]. In the case we describe here, components of the squamous cell carcinoma were sporadically detected, while the majority of the invasive carcinoma was composed of small cell type neuroendocrine carcinoma. Small cell carcinoma of the lung is considered to arise from argentaffin cells or primitive basal cells of the bronchial mucosa. Primary small cell type neuroendocrine carcinoma of the esophagus also may arise from argentaffin cells, which are present in the esophageal mucosa, or primitive basal cells of the esophageal epithelium [10]. Both of the carcinomas may have heterogeneous components, including squamous cell carcinoma [8, 10].

Most neoplastic neuroendocrine cells can be detected immunohistochemically by chromogranin A, synaptophysin, and NCAM (CD56) staining [2, 11]. In this case, most of the neuroendocrine carcinoma cells were positive for NCAM (CD56), synaptophysin, CK20, CK-CAM5.2, and bcl-2, although they were negative for chromogranin-A. These immunohistochemical findings suggest that most of the tumor cells in small cell carcinoma of the esophagus had undergone neuroendocrine differentiation.

With respect to prognosis, no significant difference has been shown in the survival of patient with pure type and combined type carcinoma [10], suggesting that prognosis depends on the small cell carcinoma component. Primary small cell type neuroendocrine carcinoma of the esophagus has been reported to have a very poor prognosis [4, 10, 12]. Beyer *et al.* [4] reported that the median survival time of 134 patients with

small cell carcinoma of the esophagus was 5.3 months, and the 1-year survival ratio was only 10%. Nichols *et al.* [12] reported that none of the patients survived longer than 2 years, and Law *et al.* [13] and Caldwell *et al.* [14] in separate studies both reported that only 1 of the 11 patients survived for more than 2 years. Takubo *et al.* [10] reported that 10% of the patients survived for more than 24 months; however, those patients had received chemotherapy in addition to surgery or radiation therapy. Mitani *et al.* [15] reported that the tumor was confined to the submucosal layer in all long-term survivors. This highly malignant behavior was also apparent in the present case. Primary small cell type neuroendocrine carcinoma is generally an aggressive tumor with early extensive and systemic metastasis, including brain metastasis [16]. Studies to establish new and more effective treatment strategies are required.

ACKNOWLEDGEMENTS

The authors express the sincere gratitude to Akihiko Serizawa M.T. (Department of Pathology, Tokai University School of Medicine) for providing technical assistance and for his cooperation in this case.

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