

Case Report

Large cell neuroendocrine carcinoma of the esophagus: report of a rare case and a literature review

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Received November 26, 2016; Accepted January 5, 2017; Epub February 15, 2018; Published February 28, 2018

Abstract: Neuroendocrine carcinoma of the esophagus, mostly comprised of the small cell type, is a rare malignant neoplasm and accounts for only 3.3% of all esophageal malignant tumors. We present a rare case of a large cell neuroendocrine carcinoma in a 73-year-old man with dysphagia. Chest computed tomography showed a 5-cm eccentric thickening of the upper thoracic esophageal wall and enlarged paratracheal lymph nodes. A McKeown operation was performed, and the resected tumor consisted of solid nests of large cells with round hyperchromatic nuclei, conspicuous nucleoli, and abundant eosinophilic cytoplasm. Immunopositivity of the tumor cells for synaptophysin and chromogranin confirmed their neuroendocrine nature. A squamous cell carcinoma or adenocarcinoma component was absent. Our report is the first description in South Korea of a tumor with typical clinical and histological features of a pure large cell neuroendocrine carcinoma of the esophagus.

Keywords: Esophagus, esophageal neoplasms, carcinoma, neuroendocrine

Introduction

An esophageal neuroendocrine tumor (NET) is a very rare neoplasm, representing only 1.3% of neuroendocrine tumors that occur in the digestive system [1] and 3.3% of all esophageal malignant neoplasms [2]. Seventy percent of esophageal NETs present as neuroendocrine carcinomas (NECs) and have a poor prognosis and low survival rate [3]. Although most of the reported NECs in the esophagus are small cell NECs, one series from the M.D. Anderson Cancer Center contained large cell NECs more than small cell NECs [4]. We now present a case of an esophageal large cell NEC that was first recognized from a biopsy as a poorly differentiated squamous carcinoma.

Case report

A 73-year-old man presented with dysphagia that had lasted for 4 months. Computed tomography demonstrated the presence of a 5-cm eccentric thickening of the wall of the upper esophagus and enlarged lymph nodes in the upper paratracheal area. A 5-cm semi-circumferential ulcerative mass in the upper esopha-

gus was observed during an esophagogastroduodenoscopy. An endoscopic biopsy of the mass showed a growth pattern of solid nests of poorly differentiated carcinoma cells and areas of necrosis. The biopsy was interpreted as a poorly differentiated squamous cell carcinoma.

A McKeown esophagogastrectomy was performed on patient. A 4.5-cm ulcerofungating mass extending to the adventitia was identified in the upper esophagus. The cut surface of the mass was grayish white, granular, and solid. Necrotic areas were also noted in the mass (**Figure 1**). A pathologic section showed the presence of anastomosing trabeculae and solid nests of pleomorphic large cells forming rosette-like structures with a palisading growth pattern and necrosis (**Figure 2A**). The cells had an abundant eosinophilic cytoplasm; large nuclei with coarse, vesicular chromatin and conspicuous nucleoli; and numerous mitoses (60 per 10 high power fields) (**Figure 2B**). There were no other components that were thought to be malignant, and the overlying squamous epithelium did not show any dysplastic feature. Poorly differentiated squamous cell carcinoma, poorly differentiated adenocarcinoma, malig-

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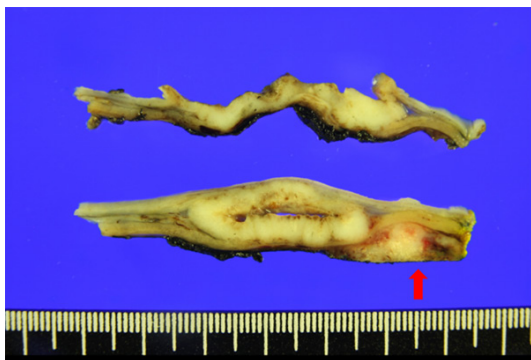


Figure 1. Gross appearance of esophageal tumor: Ulcerofungating mass in the esophagus shows grayish white colored, granular cut surface, with a necrotic area (arrow).

nant melanoma, and large cell neuroendocrine carcinoma were considered as possible differential diagnoses. Immunohistochemical studies showed that the tumor cells were positive for synaptophysin and chromogranin (**Figure 3A, 3B**), and negative for p63 and S100 protein (**Figure 3C, 3D**), supported the diagnosis of NEC. Calcitonin immunostaining was included because of the histological similarity of the tumor to large cell NEC of the larynx, but the tumor was negative (**Figure 3E**). Metastatic carcinomas were found in four paraesophageal and paratracheal nodes. The patient expired 1 month after surgery as a result of necrosis of the anastomosis site and a tracheoesophageal fistula.

Discussion

NECs of the esophagus were first reported by McKeown in 1952 [5]. However, because of their rarity, only a few studies on these neoplasms are found in the literature. According to the largest study, the majority (57.1%) of NECs were small cell type [6], and the median survival time of the patients was only 22.4 months [6]. In another study of NECs that included large cell NECs, most patients with large cell NEC had stage III or stage IV disease (85.2%) [4].

We collated all of the previous studies and case reports of large cell esophageal NEC, including those cases diagnosed as malignant carcinoid tumor, and the clinical findings of 40 patients are summarized clinical findings in **Table 1**. The mean age of the patients in these studies was 62.7 years, and the male: female ratio was 5.67. In common with other neoplasms, dys-

phagia was the most frequent chief complaint (52.5%). The second most common chief complaint was chest or abdominal pain (12.5%). Although 60% of the tumors were pure large cell NECs, the rest had mixed tumor components, of which adenocarcinoma was the most common type (32.5%). Most of the tumors were located at the mid to lower esophagus. Our case is the first report of a large cell NEC that was located at the upper esophagus. Although only 12.5% of the cases reviewed were stage I (2.5%) or stage II (10%), 82.5% were stage III (45%) or stage IV (37.5%). These results indicate the aggressive features of large cell esophageal NEC.

Except for the prevalence of Barrett esophagus in large cell NECs, previous studies have reported no significant differences in the clinical features of small cell NECs and large cell NECs [4, 7]. Although both tumor types share common features, such as a high mitotic rate, frequent necrosis, immunopositivity for neuroendocrine markers, they also possess certain distinctive histological features. The tumor cells in Large cell NECs are large (having diameters greater than those of three resting lymphocytes), and possess prominent nucleoli and coarse chromatin. In contrast, the cells of small cell NECs are small, containing inconspicuous nucleoli and fine granular chromatin.

Large cell NECs may occasionally have a mixed epithelial tumor component, of which adenocarcinoma was the most frequent type. A mixed adenocarcinoma component appeared to be associated with Barrett esophagus and a better prognosis [4].

There are other possible differential diagnoses for large cell NECs of the esophagus. Basaloid squamous cell carcinomas show a trabecular growth pattern with peripheral palisading, a pattern that is similar to large cell NECs. The nucleolus is, however, inconspicuous, and the cytoplasm is scanty. Although poorly differentiated adenocarcinomas might be difficult to distinguish from large cell NECs, they lack the presence of rosette-like structures and a palisading growth pattern.

Immunohistochemical profiling of the tumor is necessary for the differential diagnosis of large cell NECs from squamous cell carcinoma and adenocarcinoma. NECs are negative for p63, p40, CK5/6 and napsin A, while squamous cell

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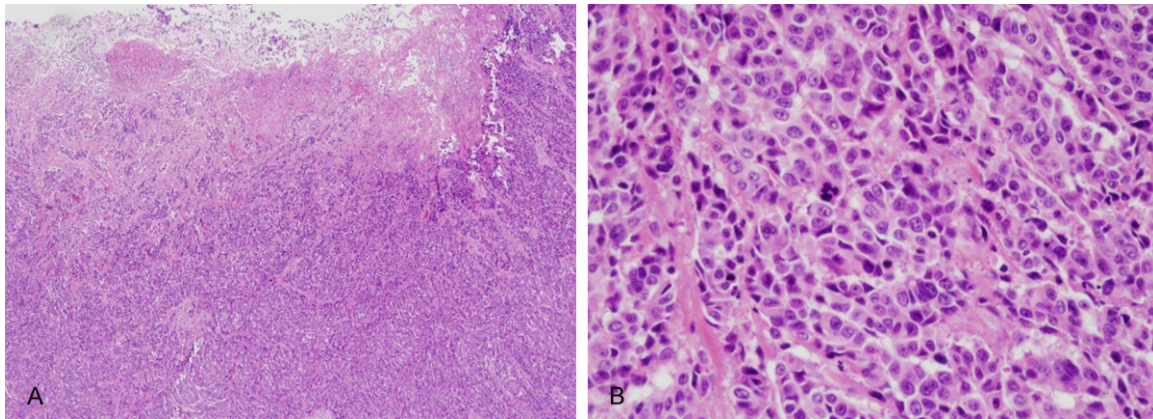


Figure 2. Histologic findings of the large cell neuroendocrine carcinoma. A. Tumor cells form anastomosing trabeculae with necrosis (H&E staining, $\times 40$). B. Tumor cells have conspicuous nucleoli and numerous mitotic counts. Atypical mitosis is also present (H&E staining, $\times 400$).

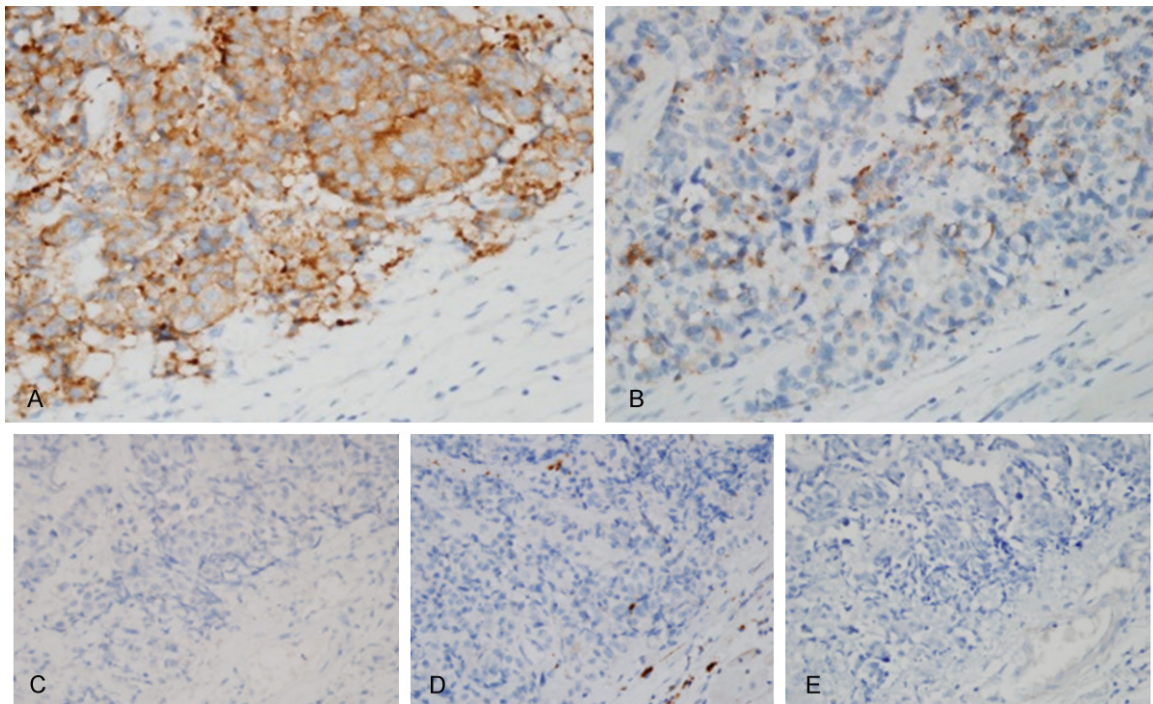


Figure 3. Immunohistochemical stains. Tumor cells show positive reaction to synaptophysin (A) and chromograin (B), and negativity to p63 (C), S100 protein (D) and calcitonin (E) ($\times 400$).

carcinomas (express p63, p40 and CK5/6) and adenocarcinomas (express napsin A) [8].

Neuroendocrine tumors arise from the diffuse components of the endocrine system in the gastrointestinal tract and lung [9]. Most of esophageal NECs are located in the middle and lower esophagus. This may be related to the presence of endocrine cells in the esophageal cardiac glands that predominate in the distal

region [10]. NECs may also originate from the Merkel cells, which are most concentrated in the middle esophagus [11]. NECs in esophagus are, therefore, assumed to arise from endocrine type cells, a situation that occurs in other organs. In the current case, the overlying squamous epithelium and submucosal glands were negative for neuroendocrine markers; therefore, the histogenesis of the present tumor is unknown.

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Table 1. Large cell neuroendocrine carcinomas of esophagus in the literature

Year	Author	Number of cases	Age	Sex	Location	Chief complaint	Mixed components	Stage at diagnosis
1989	Ready et al. [13]	1	67	F	Middle	Dysphagia	None	III
1991	Siegal et al. [14]	1	76	M	Middle	NR*	None	III
1994	Vaideeswar et al. [15]	1	55	M	Middle	Chest pain	None	II
2000	Wilson et al. [16]	1	51	M	Lower	Epigastric pain, dysphagia	Papillary adenocarcinoma	NR
2000	Gopal et al. [17]	1	62	M	Middle	Dysphagia	None	III
2008	Maru et al. [4]	27	61 [†]	M (24) F (3)	Mostly lower [‡]	Dysphagia (12) Gastrointestinal bleeding (2) NR (1) Others (12)	Adenocarcinoma (12)	I (1) II (2) III (6) IV (17) NR (1)
2013	Huang et al. [7]	5	69 [†]	M (5)	Middle (3) Lower (2)	Dysphagia (4) Chest pain (1) Abdominal pain (1)	Squamous cell carcinoma (2) Glandular features (1)	II (1) III (4)
2015	Fukuchi et al. [18]	1	65	M	Lower	Chest pain	None	III
2015	Kuriry et al. [19]	1	66	F	Middle	Dysphagia	None	IV
2016	Current case	1	73	M	Upper	Dysphagia	None	III

*NR-Not reported. [†]Average. [‡]33 of 40 patients (including small cell NEC) had tumor at lower esophagus. Exact location of tumor in large cell NEC is not separately reported.

This is the first report of a pure large cell NEC of the esophagus occurring in South Korea. The case showed typical clinical and histological features of an esophageal large cell NEC. The tumor was, however located at the proximal esophagus, which is a rare site for esophageal NEC. Unfortunately, the patient expired postoperatively because of a wound site failure, and therefore lost any chance for future adjuvant chemotherapy and cure.

There is no established treatment recommendation for esophageal NECs. Most patients have systemic disease at diagnosis because of the aggressiveness of these tumors. Conventional chemotherapy can be used for esophageal NECs, but surgery is preferred for locoregional disease. Adjuvant therapy also increased the survival time of the patients with small cell NEC [12].

Although large cell NECs are easily distinguishable from other epithelial tumors in esophagus, diagnosis may be difficult because of its rarity. The use of immunohistochemical staining should help promote both awareness and differential diagnosis of the tumor.

Disclosure of conflict of interest

None.

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