



## Primary small cell neuroendocrine carcinoma of the esophagus

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### ABSTRACT

Primary small cell neuroendocrine carcinoma of the esophagus is a very rare entity characterized by poor prognosis. Two new cases with clinicopathological characteristics are presented. In both female patients aged 62 and 66 who suffered from dysphagia for a few months, subtotal esophagectomy with lymph nodes dissection was performed. The final diagnosis was based on the pathological examination of surgical specimens. The morphology of tumors was typical with additional squamous cell carcinoma component in one case. Characteristic neuroendocrine granules were also revealed in electron microscope. Neoplastic cells were positive for pancytokeratin, chromogranin A and synaptophysin. Infiltration into the esophageal adventitia with vessel invasion and involvement of multiple regional lymph nodes was observed. The patients have died respectively nine and four months after the operation.

**Keywords:** esophagus, small cell carcinoma, neuroendocrine tumor, neuroendocrine carcinoma

### INTRODUCTION

Primary small cell neuroendocrine carcinomas (NECs) are rare lesions of the digestive system. The most common location is the esophagus, where they account 0.5-2.4% of all malignancies [2]. Since the first description by Mc Keown [7] in 1952, about 300 cases has been reported in the world literature [5]. Heavy smoking, long-standing achalasia and alcohol are thought to be the most important risk factors of primary esophageal small cell NECs [11, 12]. Their link with Barrett's esophagus has also been mentioned [9, 11].

The tumors are usually diagnosed in older patients (mean age 64 years) with male predominance (M:F=3:2) [6]. The main symptoms are dysphagia, severe weight loss and sometimes, chest pain. Ectopic hormonal secretion, including adrenocorticotrophic hormone, calcitonin, gastrin, somatostatin, and antidiuretic hormone may occur in some cases [1, 8]. Paraneoplastic neurological syndrome – sensorimotor neuropathy was also described [10]. Carcinomas are usually located in the middle and lower third of the thoracic esophagus. They form large (4 to 10 cm in diameter), fungating or ulcerating masses

with deep infiltration of the esophageal wall and adjacent organs as well as spread into regional lymph nodes at the time of diagnosis [2]. Therefore, regardless the mode of treatment the prognosis of patients with primary esophageal small cell NEC is usually poor.

In the current paper, clinical and morphological features of two new cases of primary esophageal small cell carcinomas are presented.

### MATERIALS AND METHODS

Two cases of primary esophageal small cell NECs were revealed in over 150 surgical esophageal specimens from patients diagnosed in 1995-2009 at the Department of Clinical Pathomorphology and treated at the 2<sup>nd</sup> Department of General Surgery, Medical University of Lublin. In both cases, metastases from pulmonary small cell carcinoma were excluded based on radiological examinations (AP chest X-ray, chest CT). Apart from routine hematoxylin and eosin staining, immunohistochemical reactions with selected antibodies including chromogranin A, synaptophysin, pancytokeratin (MNFI16), S100 protein, HMB45 and CD45 were applied. All antibodies and visualization system were obtained from Dako (Denmark). In one case an ultrastructure of the tumor was also studied based on archival formalin-fixed paraffin-embedded sample using typical procedure and Carl Zeiss EM900 (Germany) electron microscope.

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## RESULTS

### Case 1

A 66-year-old woman with dysphagia, appetite lost and weakness for a few months. Barium meal examination revealed the tumor located in the middle part of the thoracic esophagus (Fig. 1). The endoscopic biopsy contained mostly necrotic masses and inflammatory cells with a few small neoplastic cells suggestive for small cell carcinoma. Transthoracic subtotal esophagectomy with lymph nodes dissection was performed. In surgical specimen, fungated and ulcerated tumor 40x30x6 mm in diameter was seen. It

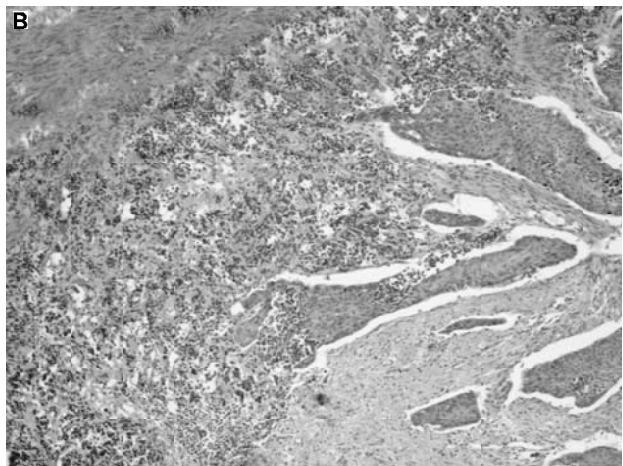
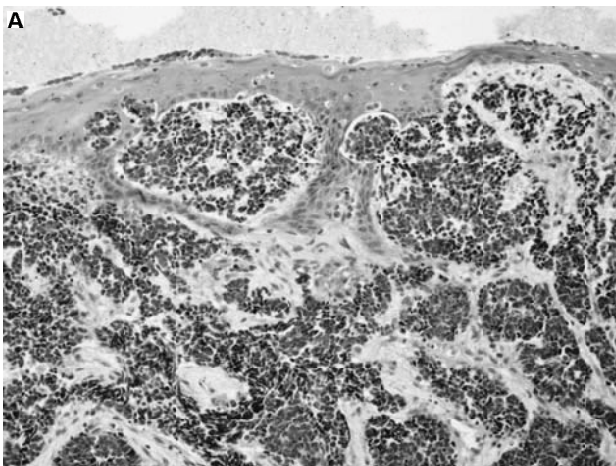


**Fig. 1.** Irregular circumferential infiltration with a constriction of the middle part of the esophagus (barium meal examination; lateral view; case 1)

was composed of solid sheets and nests formed by small, oval cells containing nuclei with “salt and pepper” appearance and scanty cytoplasm (Fig. 2A). They infiltrated superficial part of the esophageal adventitia (pT3). Vessel involvement was noted. Neoplastic cells were pancytokeratin (Fig. 3A), chromogranin A (Fig. 3B) and synaptophysin positive. Of twenty four examined lymph nodes, metastases were revealed in sixteen (pN3). Resection margins including the deep one were free of tumor (R0). The patient died nine months after the operation.

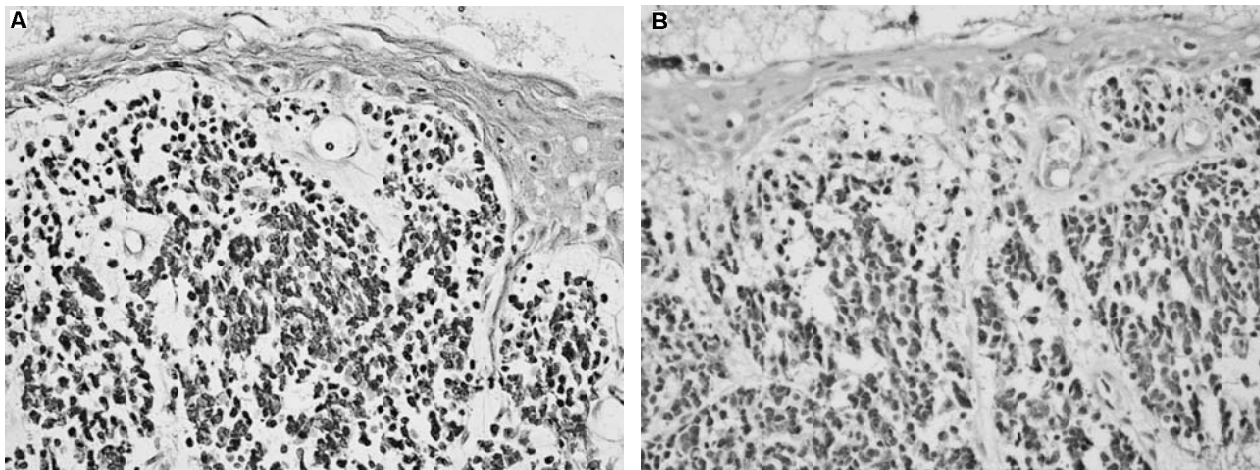
### Case 2

A 62-year-old woman suffered from dysphagia for one year, more intensive for last 2 months and loss of body weight (3-4 kg). Endoscopic examination revealed exophytic lesion localized in middle third part of the thoracic esophagus. Based on tissue samples taken by endoscopy high grade carcinoma probably of glandular origin was primary diagnosed. Transthoracic subtotal esophagectomy with 3-D lymph nodes dissection was done. In surgical specimen a 30x20x10 mm protruding and superficially ulcerated tumor was seen. Histopathological examination revealed neoplastic cells morphologically typical of small cell carcinoma, however with additional squamous cell carcinoma component (Fig. 2B). The whole wall of the esophagus was infiltrated including adventitia (pT3) and deep resection margin (R1). Neoplastic cells were also present in small vessels. Immunohistochemical reactions in small cell carcinoma component were identical like that in Case 1. Furthermore, a few small dense-core neurosecretory granules were detected in the cytoplasm of tumor cells by transmission electron microscope (Fig. 4A-B). Of thirty one lymph nodes metastases were present in fourteen (pN3). The patient died four months after the operation.

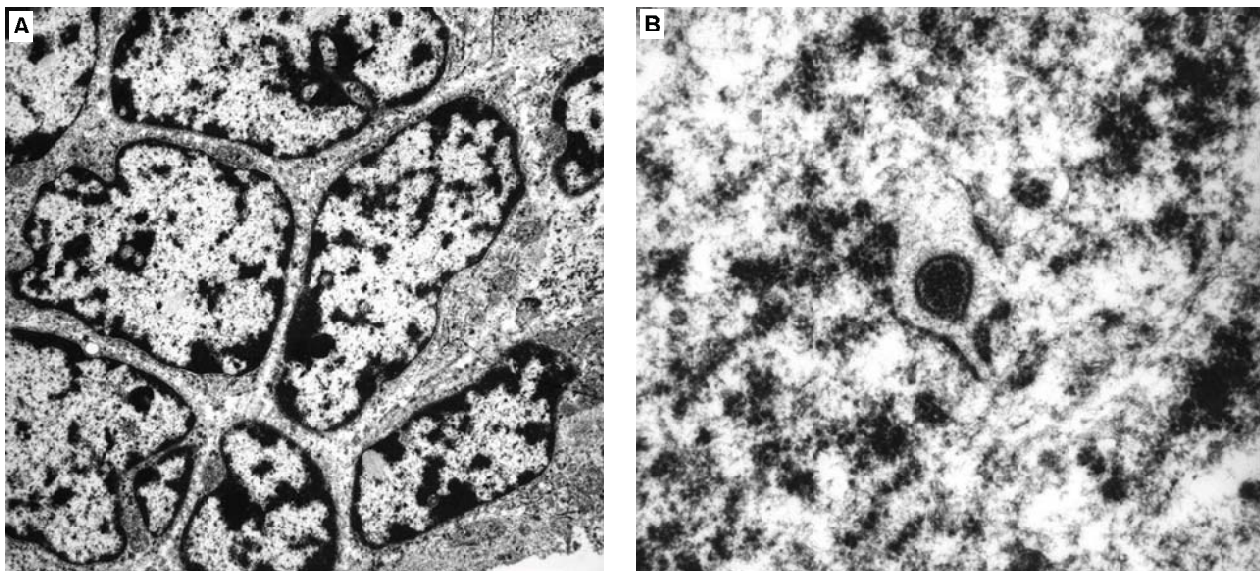


**Fig. 2.** Infiltration of esophageal wall by pure small cell carcinoma (A) and with squamous cell carcinoma component (B) (A – case 1; B – case 2; hematoxylin and eosin; objective magn. A – 10x; B – 5x)





**Fig. 3.** Positive immunostaining for pancytokeratin (A) and chromogranin A (B) in some esophageal small cell carcinoma cells (case 1; Dako EnVision<sup>TM</sup>/HRP; objective magn. 20x)



**Fig. 4.** Densely packed cells of esophageal small cell carcinoma with large slightly irregular nuclei and scanty cytoplasm (A) with single neurosecretory granule (B) (case 2; transmission electron microscope; magn. A – x4400; B – x30000)

## DISCUSSION

Vast majority of small cell carcinomas develops in the lungs. However, they are sporadically revealed in many other anatomical locations like the breast, ovary, uterine cervix, prostate, urinary bladder, kidney, liver, salivary glands, esophagus, stomach and colon [1; 12]. Although in the digestive system they are relatively common in the esophagus, their occurrence is marginal compare to esophageal squamous cell carcinoma and adenocarcinoma [1].

Morphologically primary esophageal small cell NECs are identical to its pulmonary counterpart, consisting of round to spindle-shaped cells with scanty cytoplasm, “salt and pepper” chromatin appearance, inconspicuous nucleoli as well as ultrastructural and immunohistochemical evidence of neuroendocrine differentiation [3]. Malignancies can occur in pure form or with additional components. Mc Keown [7] described admixture of squamous cell carcinoma. In relatively large series of esophageal

small cell NECs (21 cases), Takubo et al. [13] found squamous cell carcinoma or mucoepidermoid carcinoma component in 57% of tumors. However, it seems, that such morphological findings do not influence behaviour of the lesion and patients survival [13].

Immunohistochemical profile of small cell carcinomas is similar in each location [1]. They are positive for neuroendocrine markers like neuron-specific enolase (NSE), synaptophysin, chromogranin A, neural cell adhesion molecule (NCAM, CD56), transcription factor CDX2 and thyroid transcription factor 1 (TTF-1) [6, 10]. Terada [14] reported immunoexpression of KIT (CD117) and PDGFRA (platelet-derived growth factor receptor- $\alpha$ ) in esophageal neuroendocrine carcinomas (both in small and large cell carcinomas), but without identification of any mutation in both genes. Similar phenomena were noted for pulmonary small cell carcinomas [14].

Optimal therapy for primary esophageal small cell NECs has not been defined. Combined therapy – chemotherapy, radiotherapy and/or surgery is usually applied. Yamashita et al. [15] reported nine consecutive patients with that lesion treated with curative concurrent chemoradiation. All patients received four cycles of etoposide (100 mg/m<sup>2</sup>, days 1-3), combined with cisplatin (80 mg/m<sup>2</sup>, day 1), plus radiation therapy (50 Gy in daily doses of 2 Gy, 5 days/week). At the time of analysis, the median follow-up time was 10.8 months (range: 4.2-42.8 months) and 21.8 months in five living patients. Of nine patients, five (56%) archived a complete response, and the actuarial 3-year overall survival rate was 55.6%. Pantvaidya et al. [8] presented 18 patients with metastatic esophageal small cell NECs, including five patients (28%) with liver metastases. Four patients were treated with surgery, with or without chemo- or radiotherapy. Three patients were treated with chemoradiotherapy, two with chemotherapy alone, and five with radiotherapy alone. Four patients with advanced disease and poor general conditions were excluded from any treatment. The overall median survival was 6 months. Patients treated with surgery and chemotherapy had a better overall survival [8].

Morphologically and immunohistochemically primary esophageal small cell NECs are indistinguishable from small cell carcinomas of other sites [1]. Therefore in differential diagnosis metastases to the esophagus, especially from the pulmonary tumors, have to be excluded on the basis of clinical, radiological and pathological examinations [3]. Although the prognosis in small cell carcinoma remains poor, modern multimodality treatment based on chemotherapy, radiotherapy and biotherapy may positively influence survival.

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