

A case of combined small cell and squamous cell carcinoma of the larynx in a male patient in the sixth decade of life is reported. The etiopathogenesis of this combined tumor remains unclear; however, a number of hypotheses were proposed in the past including the pivotal role of Kulchitsky, squamous cells and the glandular cells. The gene mutations may also play an important role in laryngeal carcinogenesis. This unusual type of laryngeal combined carcinoma has previously been reported worldwide in only 17 cases. This is an extremely rare tumor the histological nature of which makes the diagnosis more complicated than in other types of laryngeal cancers. The diagnosis of this carcinoma is based on light microscopy and should be supported by immunohistochemical studies. In our case, the tumor was growing in the left pyriform sinus. Metastatic neck lymph nodes were found on the left side, but no distant metastases were observed. Microscopic sections revealed a combined tumor composed of small cell carcinoma neuroendocrine type and non-keratinizing squamous cell carcinoma. Positive reaction to p16, bcl-2, thyroid transcription factor 1, synaptophysin and chromogranin A in the small cell neuroendocrine type carcinoma component was observed. The cells from squamous cell carcinoma component showed positive reaction to p63, high-molecular-weight cytokeratin and cytokeratin 5/6.

Key words: larynx, combined carcinoma, small cell carcinoma, neuroendocrine type, squamous cell carcinoma.

Combined small cell and squamous cell carcinoma of the larynx

Paweł Kołodziej¹, Paweł Ostasiewicz², Piotr Ziółkowski^{1,2}

¹Division of Pathology, Wałbrzych Regional Hospital, Poland

²Department of Pathology, Wrocław Medical University, Poland

Introduction

Primary laryngeal cancer is a common malignant tumor and accounts for up to 5% of all malignant tumors in the world. Histologically, it is usually, in approximately 95%, a squamous cell carcinoma (SCC), whereas less than 5% are primary tumors deriving from glandular epithelium or from other tissues. Neuroendocrine tumors (NET) of the larynx account for less than 0.5% of all laryngeal tumors [1]. The pure form of small cell carcinoma of the larynx is also a very uncommon entity [2].

Combined small cell carcinoma with squamous cell carcinoma (SCCNET + SCC) in the laryngeal localization is an extremely rare tumor accounting for 10% of all SCCNETs [1]. It has been very rarely reported in the literature so far [3, 4].

In this paper we report a case of such a combined carcinoma in a male patient in the sixth decade of life.

Case report

A 58-year-old man presented with a 3–4 month history of worsening hoarseness and coughing. There was no history of weight loss. His entire past medical history was not significant and there was no history of any malignant tumor in his family. Neither alcohol consumption nor smoking was reported.

On laryngoscopic examination, a tumor mass was found involving the left pyriform sinus. There were also metastatic neck lymph nodes on the left side, but no distant metastases were observed. A specimen was taken from the tumor mass and the histopathologic examination revealed combined small cell carcinoma and squamous cell carcinoma (SCCNET + SCC).

The patient then underwent a total laryngectomy with lymphadenectomy. The postoperative histologic examination revealed the same combined tumor as above.

Pathologic findings. On gross examination of the surgical specimen, a 5 cm × 3 cm mass was found. The tumor was localized in the pyriform sinus and involved arytenoid muscles and arytenoid cartilage on the left side. The tumor had variable gross morphology and showed small necrotic and hemorrhagic areas, and infiltrated neighboring blood vessels. The neck lymph nodes on the left side revealed whitish, solid metastatic foci. The samples were then processed according to the routine histologic procedure.

Microscopic sections revealed a combined tumor mainly composed of small cell neuroendocrine type carcinoma and non-keratinizing squamous cell carcinoma (SCCNET + SCC). Histologic appearance of small cell carcinoma with an invasive squamous cell carcinoma part after hematoxylin and eosin staining is shown in Fig. 1. Both tumor components showed clear boundaries; however, foci of gradual transition from one to the other tumor were also detected. The margins of the specimen were free of carcinoma. The samples from neck lymph nodes showed only the metastatic squamous cell carcinoma component.

The immunohistochemical staining panel showed a diffuse positive reaction to synaptophysin and chromogranin A in the small cell neuroendocrine

type carcinoma component (Fig. 2). The cells from this component also showed positive reaction to p16, bcl-2 and thyroid transcription factor 1 (TTF-1), whereas the staining for p63 and high-molecular-weight cytokeratin (HMWCK) was negative. The cells from the SCC component showed positive reaction to p63 (Fig. 3), to HMWCK and to cytokeratin 5/6 (CK5/6), while TTF-1 and p16 were negative. All antibodies were purchased from Dako. The selection of the above antibodies was made according to the data presented by Barnes [1] where TTF-1, HMWCK and p63 are helpful in distinguishing small cell carcinoma from poorly differentiated SCC. Chromogranin together with synaptophysin allows confirmation of neuroendocrine differentiation in tumors.

Discussion

Small cell carcinoma of the larynx is an uncommon neuroendocrine tumor with particular pathologic, therapeutic, and prognostic connotations. The first case of such a lesion was reported in 1972 [2]. A large review of neuroendocrine tumors of the larynx with an update on diagnosis and treatment was published by Ferlito *et al.* in 1998 [5]. They mentioned over 500 cases of neuroendocrine tumors of the larynx in the literature reported at that moment. The diagnosis was primarily based on light microscopy and, sometimes, supported by immunohistochemical studies. Combined small cell carcinoma neuroendocrine type with squamous cell carcinoma of the larynx has been rarely reported in the literature, and is included in the current WHO classification [6]. The name “combined small cell carcinomas of larynx” was used by Ferlito *et al.* in 1985 [7]. Recently, a case of combined SCCNET with SCC was reported by Aggarwal *et al.* [6]. They found that the tumor was mainly composed of small cell neuroendocrine carcinoma nearly confined to the right side and involving the supraglottis and invasive squamous cell carcinoma component located on the left side of the larynx (mainly in the glottis). Interestingly, this side-specific distribution of the tumor was recapitulated in its metastatic nodal spread [6]. Davies-Husband *et al.* reported the first case of a laryngeal combined tumor consisting of a squamous cell carcinoma and atypical carcinoid [8]. They mentioned that primary combined neuroendocrine and squamous cell carcinoma of the larynx was even more rarely encountered, with only 14 publications of this so-called composite tumor to date. In each case, the neuroendocrine component has been small cell carcinoma [8]. The number of 14 cases has been recently increased to 17 reported cases according to the above-mentioned report by Aggarwal *et al.* [6]. The majority of patients with combined SCCNET and SCC were men in the 6th to 7th decade of life and so was our patient.

The etiopathogenesis of this combined tumor is not clear and several hypotheses have been proposed including the role of Kulchitsky, squamous and glandular cells. Based on all these theories, combined carcinomas should arise from neoplastic transformation of a differentiated precursor or a neoplastic stem cell with divergent differentiation potential [9]. Risk factors for laryngeal cancer that have been studied are as follows: tobacco smoking, alcohol consumption, radiation, paint and asbestos exposure or human papilloma virus infections. The mutation of p53 gene may also play an important role in laryngeal carcinogenesis [10].

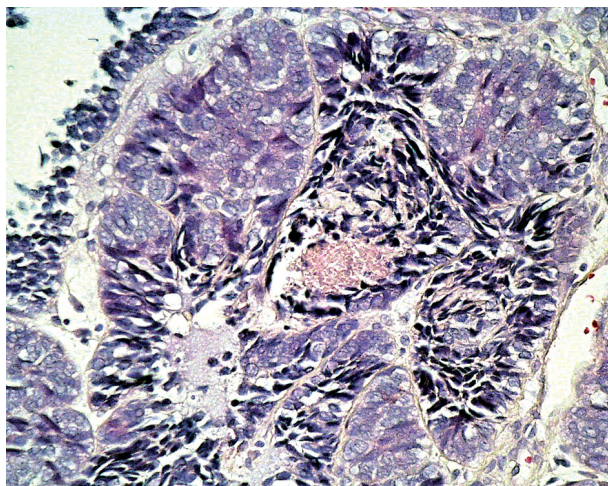


Fig. 1. Combined small cell and squamous cell carcinoma of the larynx. The microphotograph shows a collision phase of squamous cell carcinoma invasion and surrounding nests of small cell carcinoma (H&E, 200 \times)

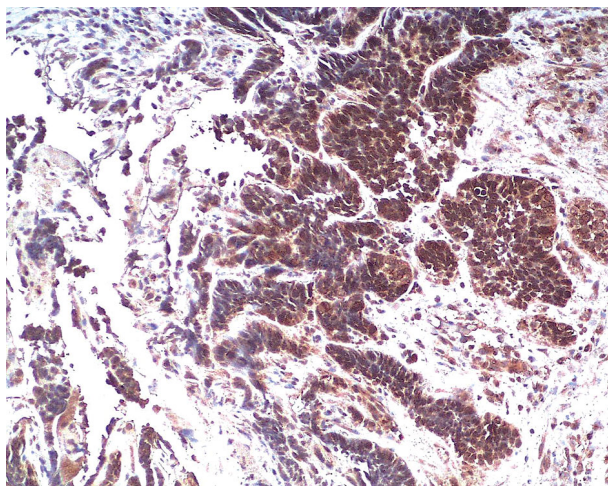


Fig. 2. Combined small cell and squamous cell carcinoma of the larynx. The chromogranin reactivity in the small cell carcinoma component is seen in this figure (ABC method, 200 \times)

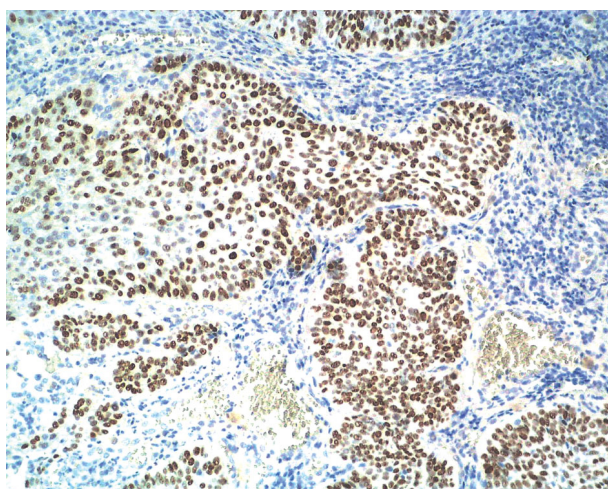


Fig. 3. Combined small cell and squamous cell carcinoma of the larynx. The p63 reactivity is seen in the nuclei of the cells of the squamous cell carcinoma component (ABC method, 200 \times)

In a large survival analysis for non-squamous cell carcinoma of the larynx, Lin *et al.* found that from 140 supraglottic non-SCC cases, 25 were of neuroendocrine, and 25 other cases of small cell type origin and not even one was reported as a combined SCCNET with SCC [11]. The biological behavior of SCCNET with SCC in the larynx seems to be similar to that of the pure laryngeal small cell carcinoma, neuroendocrine type. The clinical course of all the cases reported so far was fatal with spread of disease to distant sites and mean survival rate up to 2 years.

This report emphasizes the value of precise pathologic diagnosis in differentiation of laryngeal tumors, and the need for thorough pathologic evaluation of combined laryngeal cancers.

References

1. Barnes L Neuroendocrine tumors. In: WHO classification of tumors, Pathology and Genetics, Head and Neck Tumors. Barnes L, Eveson JW, Reichart P, Sidransky D (eds.). WHO Press, Geneva 2004; 135-9.
2. Olofsson J, van Nostrand AWP. Anaplastic small cell carcinoma of larynx: case report. *Ann Otol Rhinol Laryngol* 1972; 81: 284-7.
3. Jaiswal VR, Hoang MP. Primary combined squamous and small cell carcinoma of the larynx. A case report and review of the literature. *Arch Pathol Lab Med* 2004; 128: 1279-82.
4. Barbeaux A, Duck L, Weynand B, Desuter G, Hamoir M, Gregoire V, Baurain JF, Machiels JP. Primary combined squamous and small cell carcinoma of the larynx: report of two cases and discussion of treatment modalities. *Eur Arch Otorhinolaryngol* 2006; 263: 786-90.
5. Ferlito A, Barnes L, Rinaldo A, Gnepp DR, Milroy CM. A review of neuroendocrine neoplasms of the larynx: update on diagnosis and treatment. *J Laryngol Otol* 1998; 112: 827-34.
6. Aggarwal G, Jackson L, Sharma S. Primary combined small cell carcinoma of larynx with lateralized histologic components and corresponding side-specific neck nodal metastasis: report of a unique case and review of literature. *Int J Clin Exp Pathol* 2011; 4: 111-7.
7. Ferlito A, Recher G, Caruso G. Primary combined small cell carcinoma of the larynx. *Am J Otolaryngol* 1985; 6: 302-8.
8. Davies-Husband CR, Montgomery P, Premachandra D, Hellquist H. Primary, combined, atypical carcinoid and squamous cell carcinoma of the larynx: a new variety of composite tumour. *J Laryngol Otol* 2010; 124: 226-9.
9. Ferlito A. Diagnosis and treatment of small cell carcinoma of the larynx: a critical review. *Ann Otol Rhinol Laryngol* 1986; 95: 590-600.
10. Jin X, Zhou L, Zhao A. Mutants of p53 gene presence in laryngeal carcinoma and adjacent histopathologically normal tissue. *ORL J Otorhinolaryngol Relat Spec* 2000; 62: 140-2.
11. Lin HW, Bhattacharyya N. Staging and survival analysis for nonsquamous cell carcinomas of the larynx. *Laryngoscope* 2008; 118: 1003-13.

Address for correspondence

Piotr Ziółkowski MD, PhD
Department of Pathology
Wrocław Medical University
ul. Marcinkowskiego 1
50-368 Wrocław
tel. +48 71 784 12 25
fax +48 71 784 00 57
e-mail: ziolkows@interia.pl

Submitted: 9.05.2011

Accepted: 18.01.2012