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.
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 (CKS/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 carcinoma [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].
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


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