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Simultaneous tumours of the larynx with the same histology: a case report and review of the literature

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Abstract
Synchronous laryngeal malignancies are extremely uncommon. To the best of our knowledge, only four cases of primary synchronous squamous cell carcinoma (SCC) of the larynx are available in the literature. We report the case of a 52-year-old patient with simultaneous spindle-cell carcinoma and SCC *in situ* of the larynx. The pathogenesis, treatment and prognosis of this rare occurrence have been discussed.

Key words: Larynx; Carcinoma; Neoplasms; Multiple Primary

Introduction

The development of more than one independent malignant tumour in the same patient (multiple primary malignancies) has been extensively documented. Two primary malignant tumours that are diagnosed 6 months or more apart are defined as metachronous or subsequent. Synchronous primary malignant tumours are two lesions diagnosed within a 6-month period. Simultaneous primary malignant tumours are a subclass of synchronous primary malignancies and are defined as those separate malignancies, which are diagnosed at the same time.

Reviewing 1 104 269 cancer patients in the literature, Demandante *et al*.[1] disclosed a mean incidence of multiple primary malignant tumours of 3.9 per cent (ranging between 0.734 per cent and 11.7 per cent). Considering head and neck malignancies, the rates of developing synchronous carcinomas of the head and neck mucosal sites seem to be correlated with initial head and neck mucosal sites. Evaluating a series of 1112 patients with head and neck squamous cell carcinoma (SCC), Erkal and colleagues[2] disclosed 77 patients (7 per cent) presenting with synchronous carcinomas of the head and neck mucosal sites. Distribution of synchronous carcinoma occurrence according to initial head and neck site of first diagnosed malignancy was: oropharynx 54 cases (70 per cent), hypopharynx 18 cases (23 per cent) and supraglottic larynx 5 cases (7 per cent).

Synchronous malignancies with the same or different histology developing together in the larynx are very uncommon.

Case report

A 52-year-old man was admitted to the Department of Otolaryngology, Head and Neck Surgery, Padova University with a 4-month history of hoarseness, dysphonia and progressive dyspnoea. The patient was a school teacher with no history of cigarette smoking or alcohol consumption.

An endoscopic evaluation of the larynx revealed a large whitish mass (1.5 cm in diameter) covered by macroscopically non-ulcerated mucosa involving the anterior commissure and the anterior third of the left vocal fold (Figure 1). No enlargement of the cervical lymph nodes was found. Chest X-ray was negative.

After a fibroscopic endotracheal intubation, a microlaryngoscopy with laryngeal mass excision was performed. The histological examination of the specimen showed a spindle-cell carcinoma. The patient then underwent left cordectomy. A right vocal fold leucoplastic lesion was also biopsied. Biopsies of the macroscopically healthy tissue of the anterior commissure were performed. Histopathological evaluation confirmed the diagnosis of spindle-cell carcinoma of the left vocal fold (Figure 2). *In situ* SCC of the right vocal fold was also diagnosed (Figure 3). Anterior commissure biopsies were negative. The histopathologist concluded the presence of simultaneous spindle-cell carcinoma and *in situ* SCC of the larynx. Neck sonography did not show clinically metastatic lymph nodes. Radiotherapy (68 Gy in 34 treatments) was planned.

At 2-year follow-up control, there was no evidence of recurrent disease.

Discussion

Synchronous laryngeal malignancies are extremely uncommon. The occurrence of primary synchronous malignant tumours of the larynx with different histology has been documented.

The first report is probably that of Mills *et al*.[3] who described synchronous laryngeal SCC and Hodgkin's disease. Coexistence of laryngeal SCC and lymphoma was also reported by Elisei *et al*.[4] (histiocytic lymphoma) and Hisashi *et al*.[5] (MALT-type lymphoma). Rare cases of synchronous SCC and sarcoma of the larynx have been described. Srinivasan and Talvalkar[6] reported synchronous laryngeal SCC and rhabdomiosarcoma occurrence. Two

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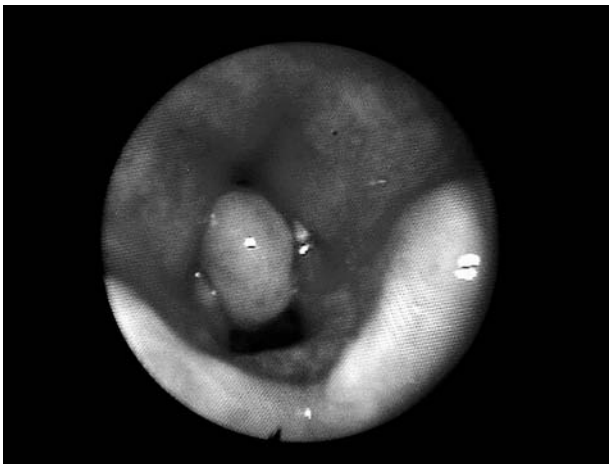

FIG. 1
Endoscopic appearance of the left vocal fold lesion.

cases of SCC and chondrosarcoma of the larynx were described by Issa[7] and Medina-Banegas *et al*.[8] Ferlito[9] described one case of laryngeal synchronous *in situ* SCC and malignant pleomorphic fibrous histiocytoma. Synchronous laryngeal SCC and adenocarcinoma were observed by Komorn *et al*.[10] and Obermayer and Ramadan.[11] Eusebi *et al*.[12] and Ferlito[13] reported three cases of synchronous SCC and oat cell carcinoma of the larynx.

To the best of our knowledge, only anecdotal cases of primary synchronous malignant tumours of the larynx with the same histogenesis are presented in the literature. Reporting three cases of multiple laryngeal SCCs (two metachronous and one synchronous), Rabbett[14] described the case of a 47-year-old male patient presenting simultaneous SCC of the right vocal fold and *in situ* carcinoma of the ipsilateral ventricular band. Heiner[15] reported the case of a patient who presented three distinct and separate primary simultaneous SCCs: an SCC of the cervical trachea, an SCC of the left vocal fold and a carcinoma *in situ* of the right aryepiglottic fold. Croce and colleagues[16] reported a case of synchronous laryngeal SCC and verrucous SCC. Finally, Ossoff and Bytell[17] described the case of a 39-year-old man who had three coexistent neoplasms of the larynx: a squamous papilloma, a verrucous carcinoma and an SCC.

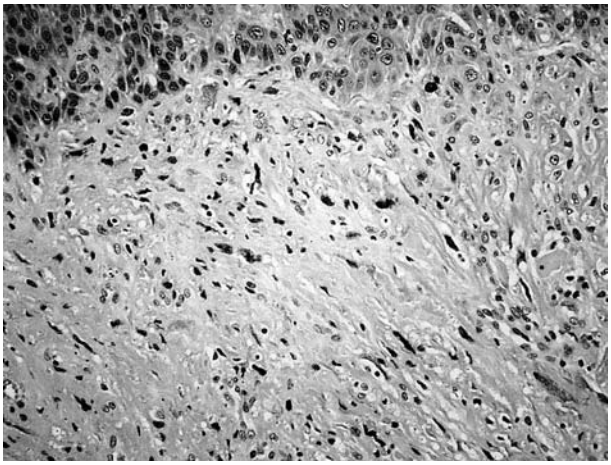

FIG. 2
Laryngeal spindle-cell carcinoma (left vocal fold) (haematoxylin-eosin staining; original magnification 220x).

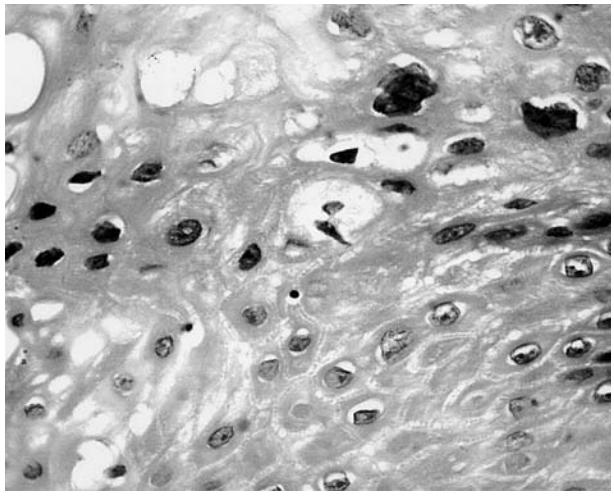

FIG. 3
In situ squamous cell carcinoma of the right vocal fold. At higher magnification, the shift from neoplastic tissue can be noticed, represented by two malignant neoplastic cells (above) to normal epithelial cells (below) (haematoxylin-eosin staining; original magnification 650x).

Various terms have been used to describe spindle-cell squamous carcinomas, reflecting the controversy surrounding their histogenesis. These kinds of tumours are referred to as malignant bimorphic tumours composed of an SCC with spindle-cell stroma that may vary from bland to pleomorphic. They are probably squamous carcinomas with spindle-cell morphology, and thus might be better described as 'biphasic variants of SCC', in which the pseudosarcomatous spindle-cell components dominate.[18] Considering spindle-cell carcinoma to be a morphological variant of SCC, we have included our case in the list of synchronous laryngeal malignancies with the same histology.

Total laryngectomy was performed in all the cases of synchronous laryngeal SCCs disclosed from literature review (four cases). Our patient underwent left cordectomy followed by radiotherapy. No data about radiotherapy have been reported by the other authors. Two out of the four previously reported cases underwent unilateral neck dissection.[15,16] The very limited number of reported cases does not allow analysis of the prognosis of synchronous laryngeal SCCs. Considering the cases with available follow-up data,[15,16] including the present one, all the patients were disease-free at the last control stage (median follow-up time 24 months).

The development of second primary tumours, either synchronous or metachronous, in the larynx may be due to genetic abnormality or to field change.[19] The first hypothesis assumes a germ-line mutation (first hit) that primes the somatic cells to environmental carcinogenesis (second hit). In the process of field change the entire epithelium at risk is exposed to combined carcinogenetic insults (mostly an immoderate use of tobacco and/or alcohol) and, as a result, there is a relatively high probability of developing multiple foci of premalignant and malignant lesions.[20] Recent studies have tried to describe the process of field cancerization from a molecular viewpoint, supporting the carcinogenetic model in which the development of a field with genetically-altered cells plays a central role. The model of head and neck SCC carcinogenesis proposed by Braakhuis *et al*.[21] focused on an initial phase when a stem cell acquires genetic alterations and forms a 'patch' which is a clonal unit of altered 'daughter cells'. After additional genetic

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alterations the patch becomes an expanding field which is an epithelial lesion consisting of cells with cancer-related genetic alterations. By virtue of its grown advantage, a proliferating field gradually displaces the normal mucosa. As the lesion becomes larger, additional genetic hits lead to the development of one or more tumours within a contiguous field of pre-neoplastic cells. Different clones diverge at a certain time point with respect to genetic alterations but share a common clonal origin. A field of genetically-altered cells subject to carcinogenetic risk factors also characterizes most of the patients after the radical removal of a malignant tumour.

- **This is a case report of a patient who developed synchronous tumours in the larynx**
- **The possible pathophysiology of this occurrence is explored**

Interestingly, the combined persistence of this genetically-altered field and these risk factors could explain not only the occurrence of synchronous laryngeal SCCs but also the relatively significant incidence of laryngeal association of SCC and oat cell carcinoma (neuroendocrine carcinoma). The significant role of cigarette smoking in oat cell carcinoma carcinogenesis has been confirmed.

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