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Composite primary small cell carcinoma and squamous cell carcinoma of the supraglottic Larynx

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Abstract: Combined primary small cell carcinoma and squamous cell carcinoma is a rare carcinoma of larynx of which less than 20 cases reported in the English literature. We report a case of a 62-year--old man, who presented with a history of hoarseness of his voice and dysphagia. He underwent flexible naso endoscopy which revealed a mass involving the right side of his larynx, subsequent to which he underwent direct laryngoscopy and biopsy of the mass. Histopathological examination of the specimen showed features consistent with composite small cell carcinoma and squamous cell carcinoma of the larynx. Based on computed tomography scan findings and laryngoscopy assessment, his tumor was staged T4N2cM0. He was planned to undergo chemo-radiation. Pursuant to receiving two cycles of chemotherapy he was found to have developed pulmonary metastatic nodules. He was next treated by means of palliative chemo-radiotherapy and died 9 months following the initial diagnosis.

Keywords: Small cell cancer of Larynx, Neuroendocrine tumour of Larynx, Primary cancer of Larynx, composite small cell carcinoma with squamous cell carcinoma.

INTRODUCTION:

Approximately 99% of laryngeal tumours are squamous cell carcinoma (SCC) [1]. Laryngeal tumours are most commonly found in the region of the glottis, namely, the true vocal cords. Laryngeal tumours tend commonly to present with change in voice quality (i.e. hoarseness). The vast majority of patients with laryngeal tumour have a history of smoking, and alcohol consumption is considered a significant co-factor for the disease [2]. Laryngeal neuroendocrine carcinomas (LNECs) are rare but are the most common non-squamous tumour of this organ [3], which can be divided in two broad categories based on the tissue of origin: epithelial and neural origins. Epithelial origin neuroendocrine tumours can be subdivided into typical carcinoid, atypical carcinoid, large cell neuroendocrine carcinoma and small cell neuroendocrine carcinomas [4]. The neural origin category of neuroendocrine tumour of the larynx is classified as a paraganglioma, which is invariably benign [4]. These subtypes can be differentiated from one another on the basis of the histological appearances of the lesions. The combined or composite small cell neuroendocrine carcinoma is a tumour in which there is a definite component of small cell carcinoma together with squamous cell carcinoma and/or adenocarcinoma [5, 6]. This article reports of a case of primary composite small cell carcinoma of Larynx and squamous cell carcinoma and a brief discussion of the literature. We would recommend that clinicians who encounter this tumour should report such tumours so that the biological behaviour of the tumour would be known to enable a consensus opinion to be decided on the management options in the future.

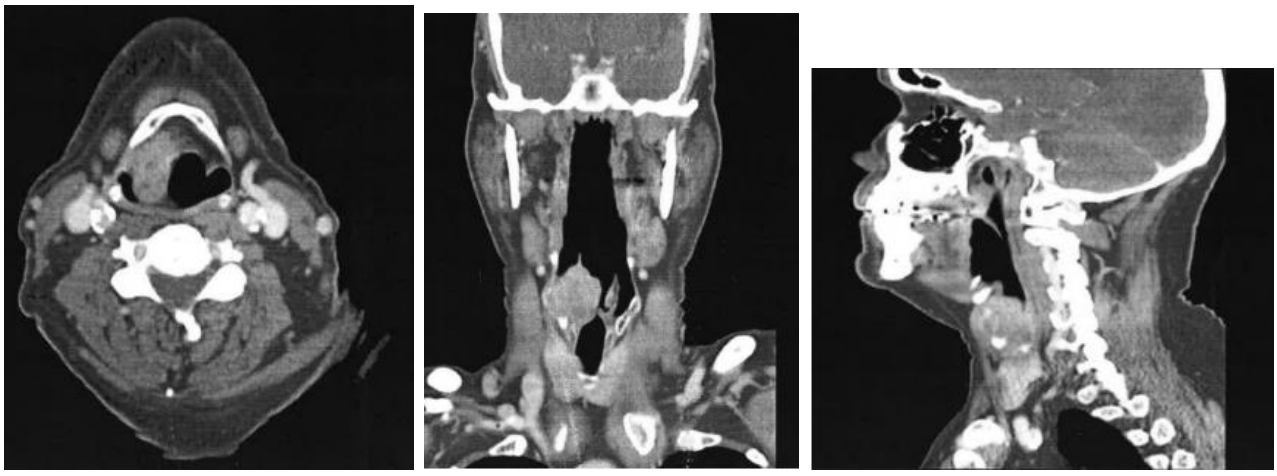
CASE REPORT:

A 62-year-old man presented with seven weeks history of hoarseness of his voice. He stated that pursuant to his development of hoarseness in his voice, he subsequently, also developed progressive dysphagia and food sticking at the back of his throat. He had a history of having been smoking 8 to 10 cigarettes for thirty years. He also had a history of alcohol consumption. He had fibre optic laryngoscopy which showed an ulcerative, right-sided laryngeal mass. The mass was completely fixed to the surrounding tissue. There were no lymph nodes palpable clinically.

He had computed tomography (CT) scan of the head, neck and thorax which showed a 3.5 cm x 3.2 cm x 3.7 cm laryngeal mass (see figures 1a, 1b and 1c,

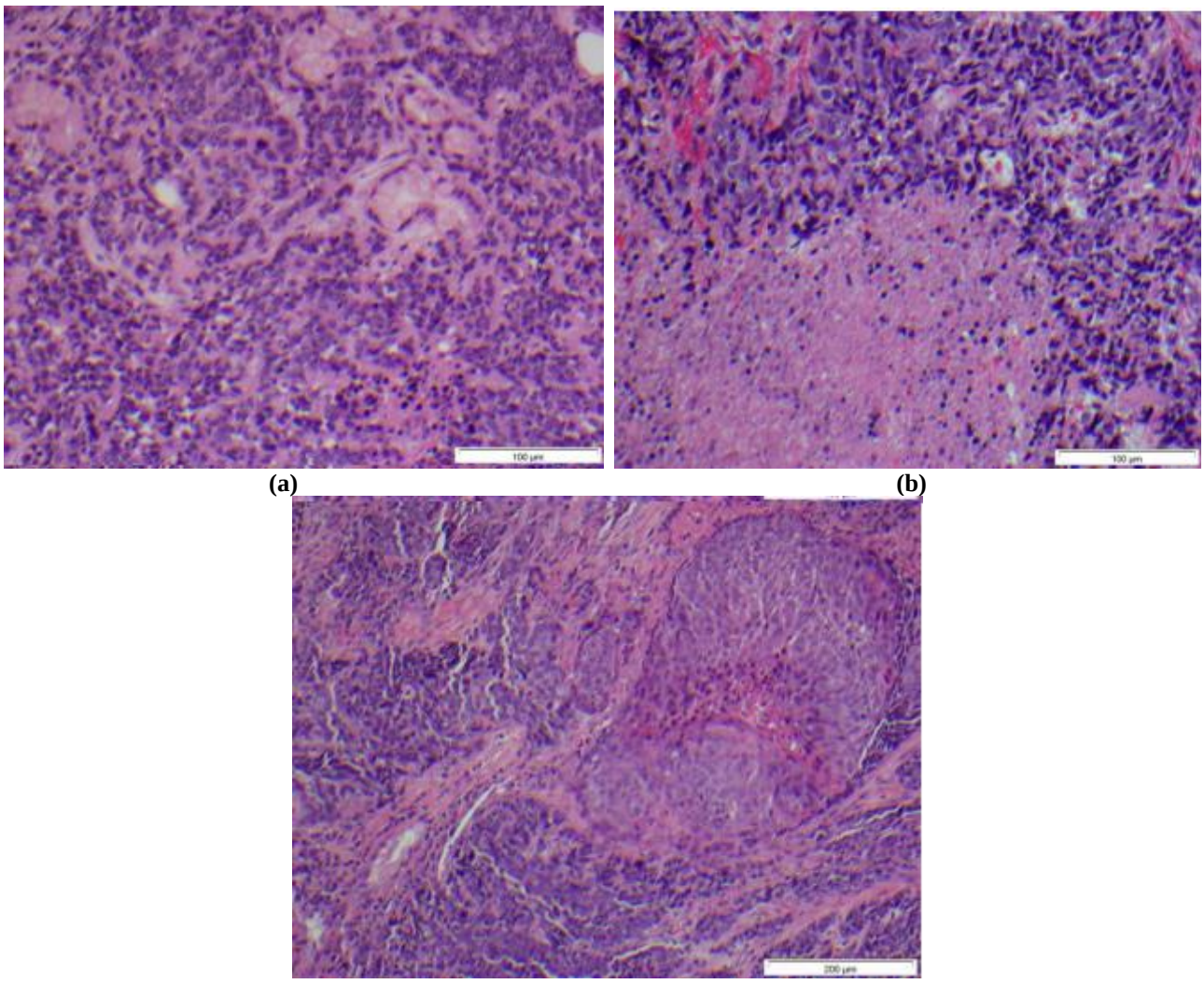
which illustrate the CT scan features of the mass in various sections). The CT scan of the neck revealed bilateral level III pathological neck nodes which measured 8.1 mm x 6.1 mm. His CT scan of the thorax was normal at the time of his presentation.

He underwent laryngoscopy and biopsies taken from the laryngeal tumour mass. Histological examination of the biopsy specimens showed that the bulk of the tumour was composed of islands of small cells with hyper chromatic nuclei which exhibited nuclear moulding. The nested basaloid tumour exhibited nuclear pleomorphism, and hyperchromatism as illustrated (see figure 2a). The biopsy specimen also showed crush artefact with areas of tumour necrosis (see figure 2b) as well as a second component of squamous carcinoma (see Figure 2c) which was associated with atypia within the surface epithelium. Immunohistochemistry studies of the tumour mass had shown that the squamous component had exhibited diffuse strong positive staining for CD56, 34βE12, CK5/6, p63 and p40 (see figure 3a which shows positive staining for CD56). Immunohistochemistry studies of the tumour also showed that the small cell component of the tumour was negatively stained for the aforementioned markers but stained positively with AE1/3, synaptophysin. The small cell component of the tumour also exhibited focal positive staining for chromogranin (see figure 3b). The MIB1 proliferation index of the tumour was in the range of 80%. The microscopic appearances and the immunohistochemistry characteristics of the tumour were adjudged to be consistent with a diagnosis of a small cell carcinoma (Grade 3 neuroendocrine carcinoma) with a small component of more conventional squamous cell carcinoma. The case was discussed at the local multi-disciplinary team meeting and based upon the clinical features, the radiological imaging characteristics and the pathological findings of the tumour the tumour was staged as T4N2cM0. Based upon recommendations obtained at a Head and Neck multi-disciplinary team meeting, he was initially treated by means of induction chemotherapy followed by radiotherapy. He received 3 cycles of Cisplatin 75 mg/m2, Docetaxel 75 mg/m2, 5FU 750 mg/m2. After he had received 3 cycles of chemotherapy he had a repeat CT scan of his neck and thorax which showed the appearance of new pulmonary micro-nodules (see figure 4 which illustrates the CT scan of thorax showing pulmonary nodules). Resistance to chemotherapy is generally considered as poor prognostic factor and given the aggressive nature of disease, palliative radiotherapy was given. His disease continued to progress after palliative chemo-radiotherapy and he eventually died 9 months after his initial diagnosis.



(a) **(b)** **(c)**

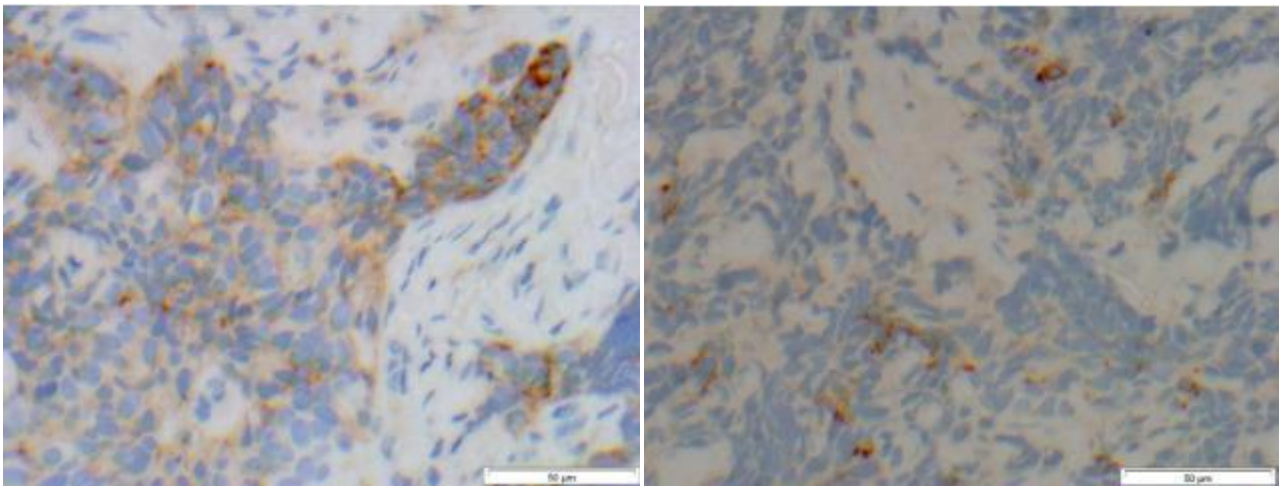
Fig-1: showing CT scan of Neck showing large mass of right side of larynx involving supraglottic, glottis and subglottic region. 1a axial section; 1b coronal view; 1c sagittal view



(a) **(b)**

(c)

Fig-2a: Sections show nested basaloid tumour showing nuclear pleomorphism, and hyperchromatism 2b: Sections show focal necrosis, crush artefact and nuclear moulding 2c: Sections show a focus of conventional squamous cell carcinoma adjacent to the small cell carcinoma



(a) **(b)**

Fig-3a: Immunohistochemical staining showing focal CD56 positivity in the small cell carcinoma component. 3b: Sections show focal chromogranin reactivity in the small cell carcinoma component

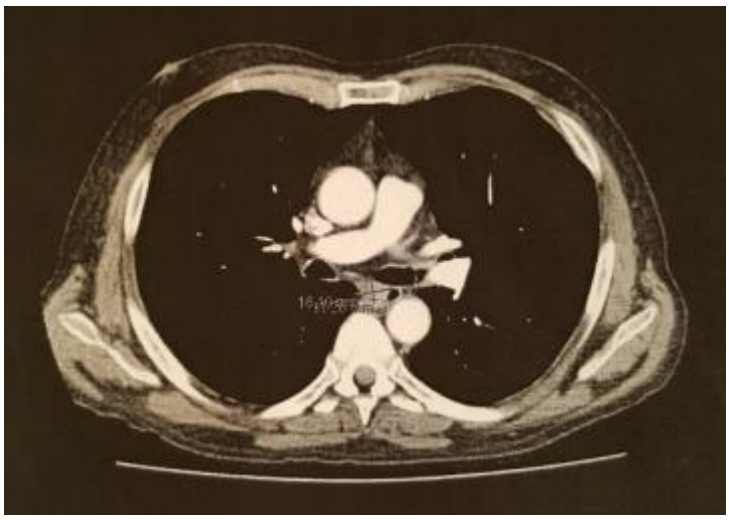


Fig-4: CT chest showing pulmonary micronodules following chemotherapy

DISCUSSION:

In 1981, Mills *et al.;* [7] analysed histologic features of 2 cases of small cell carcinoma of larynx which showed the presence of both squamous features (intra cytoplasmictono filaments and desmosomes) as well as dense core granules in the tumor cells. One case revealed a biphasic light microscopy consisting of both small cell and squamous cell components. In year 1985 for the first time term "combined small cell carcinomas of larynx" was used by Ferlito *et al*.; [6]. Very limited literature is reported due to rarity of disease [1, 5, 8]. In case of combined carcinoma generally bulk of tumour is squamous with limited tissues derived from glandular cell or other tissues [5]. But this case is unique because bulk of tumor was small cell carcinoma with smaller component of squamous cell carcinoma.

There are several theories about development of composite small cell and squamous cell carcinoma. These hypotheses are based on role of glandular, squamous and Kulchitsky cells. Etiology is based on neoplastic transformation of a differentiated precursor or a neoplastic stem cell with divergent differentiation potential. P53 gene mutation can play a key role in carcinogenesis [5]. Risk factors include smoking, alcohol consumption, tobacco, radiation, paint, human papilloma virus infections and asbestos infections [5]. Composite small cell and squamous cell carcinoma is extremely rare and very limited number of cases has been reported, and to our best knowledge less than 20 cases have been reported so far. An experimentally supported theory suggests transformation of neoplastic stem cells into two distant cell types, which are structurally and morphologically different [7]. So it seems that either a neoplastic stem cell or transformation of a differentiated precursor results in development of composite cancer cells [7].

Majority of patients found to have combined small cell and squamous cell carcinoma were male in sixth and seventh decades of life were in reported cases [7]. Common site of involvement seems to be right hemilarynx which may involve into glottis and supraglottic region [7].

Composite small cell carcinoma and squamous cell carcinoma seems to be similar to pure small cell carcinoma in terms of biological behaviour [5]. Nearly all of patients in reported cases died with mean survival rate up to 2 years 5. Nodal spread and distant metastasis is common [5]. Small cell component has major impact in terms of rapid growth and metastatic potential [7]. Direct tumor spread and lymphatic spread is common but blood stream spread is seen in advance cases [7].

Management strategy of composite small cell carcinoma and squamous cell carcinoma is the same as pure small cell carcinoma[3]. Chemotherapy and radiotherapy are considered as main modalities of treatment due to aggressive nature of disease and poor prognosis, although the regimen of chemotherapy is not well established [3]. Surgery in the form of laryngectomy is also one of treatment strategies [3].

Prognosis of composite small cell carcinoma and squamous cell carcinoma seems similar to pure small cell carcinoma in terms of biological behaviour [5]. Nearly all of patients in reported cases died with mean survival rate up to 2 years [5]. Nodal spread and distant metastasis is common [5]. Gnepp *et al.;* [9] in 1991 stated the following: (a) more than 90% of patients with this tumor develop metastatic disease; (b) The most common sites of metastatic spread of this very aggressive neoplasm are the cervical lymph nodes, liver, lung, bones, and bone marrow. Small cell component has major impact in terms of rapid growth and metastatic potential [7]. Direct tumour spread and lymphatic spread is common but blood stream spread is seen in advance cases [7]. In a review by Gnepp *et al.;* [9] found 73% of patients with laryngeal small cell neuroendocrine carcinoma died of disease with widespread metastases, with a mean survival time of 9.8

months (range, 1–26 months). The 2-year and 5-year survival rates were reported to be 16% and 5%, respectively.

CONCLUSION:

Composite primary small cell cancer and squamous cell cancer of Larynx is rare. Diagnosis is based on histology and immunoreactivity. Composite primary small cell and squamous cell carcinoma should be differentiated from other neuroendocrine tumours of larynx as management and prognosis varies significantly among different types laryngeal tumors. Biological behaviour is aggressive which results in nodal involvement and distant metastasis. Clinical course is fatal in majority of cases. Meta-analysis of large number of cases is required to determine the best treatment modality.

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