

Case Report

Small cell neuroendocrine carcinoma of subglottis: a case report

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Received: 22 February 2021

Accepted: 03 April 2021

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ABSTRACT

Small cell carcinoma is an uncommon type of malignant epithelial neuroendocrine neoplasm. It is most commonly of pulmonary origin and only less than five percent of all tumours are extrapulmonary. Esophagus, stomach, colon and rectum, gall bladder, head and neck, urinary bladder, prostate, skin and cervix are the most common extrapulmonary sites. Small cell carcinoma of larynx accounts for less than one percent of all laryngeal neoplasms. It is a highly aggressive neoplasm with poor prognosis. It most commonly affects supraglottis in males who are heavy smokers in their sixth and seventh decades. Various paraneoplastic syndromes can also be associated with the neoplasm. More than 90% of small cell laryngeal neoplasms present with metastatic disease. Surgery is not considered the initial treatment of choice; concurrent chemo radiotherapy is proven to provide longer survival. We report the rare case of extrapulmonary small cell neuroendocrine tumour in subglottis in a non-smoker female patient.

Keywords: Small cell neuroendocrine carcinoma, Laryngeal neoplasms, Extrapulmonary, Subglottis

INTRODUCTION

More than 90 per cent of all malignant tumours of larynx are squamous cell carcinomas. Neuroendocrine tumour is a non-squamous type of laryngeal neoplasm, constituting less than one percent of all primary laryngeal tumors.¹ According to the World Health Organization, neuroendocrine tumours of larynx are of four subtypes: typical carcinoid tumour, atypical carcinoid tumour, small cell neuroendocrine tumour and paraganglioma. Small cell carcinoma is an uncommon type of primary laryngeal tumour and it accounts for 0.5 percent of all laryngeal malignancies.² It is a highly aggressive tumour and should be considered as a disseminated condition at the time of initial diagnosis itself.³ Supraglottis is the most frequent site of laryngeal small cell carcinoma and subglottic small cell carcinoma is extremely rare. Very few cases of subglottic small cell carcinoma have been reported in the literature. Concurrent chemoradiotherapy is the primary modality of treatment and has shown to provide longer survival.¹ This tumour is known to have bleak prognosis even when diagnosed in the initial stages. The five year

survival rate is similar to that for small cell lung cancer and does not correlate well with the size of the tumour.⁴

In this report, we present the case of subglottic small cell carcinoma in a middle aged female.

CASE REPORT

A 45 year old female who is a non-smoker, with no remarkable medical history, presented to the department of Otorhinolaryngology with worsening dysphonia for 2 months. She gave no history of vocal abuse, dyspnea, stridor, dysphagia or neck swellings. No history of previous neck surgeries. Laryngoscopy revealed a smooth submucosal mass in subglottis below the right true vocal fold (Figure 1), while supraglottis and glottis appeared normal. Both vocal cords were mobile. There was no palpable cervical lymph node at the time of clinical physical examination. A contrast enhanced computed tomography (CECT) of neck and thorax revealed a mild enhancing soft tissue density nodule measuring 1.4×1×1.3 cm (AP×T×SI) in the right subglottic region which was not

separately visualized from the right true vocal fold (Figure 2). The lesion was causing significant luminal narrowing of infraglottic trachea, but not crossing the midline. There was no cartilage involvement. Small bilateral level II lymph nodes were noted. Patient underwent elective tracheostomy on-table followed by microlaryngoscopic surgery and excision of the mass under general anesthesia; the specimen was sent for histopathologic examination. The postoperative course was uneventful and she was discharged following closure of tracheostomy. Follow up was advised.



Figure 1: Preoperative laryngoscopic image showing a single smooth submucosal growth in subglottis below the right true vocal fold.

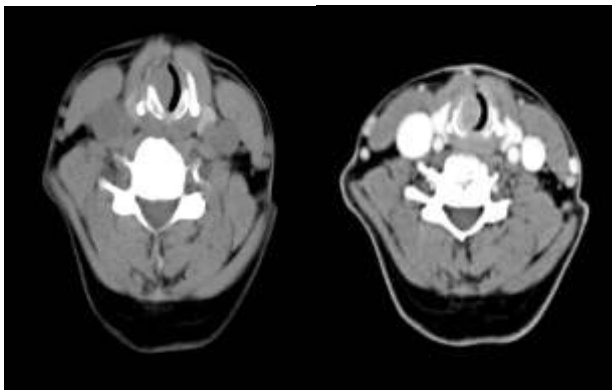


Figure 2: Computed tomography scan of neck (plain and contrast) showing the subglottic mass.

Histopathologic examination revealed tumour cells with high nuclear-cytoplasmic ratio arranged in sheets and small nests separated by thin fibro vascular septae (Figure 3). Tumour cells showed scant eosinophilic cytoplasm, round to elongated nuclei with stippled chromatin and inconspicuous nucleoli. Nuclear pleomorphism was present; mitotic and apoptotic figures were noted. In some areas, they showed crushing and moulding of nuclei; areas of necrosis seen. Possibilities of poorly differentiated (small cell) carcinoma or non-Hodgkin's lymphoma were suggested and hence immunohistochemical study was performed.

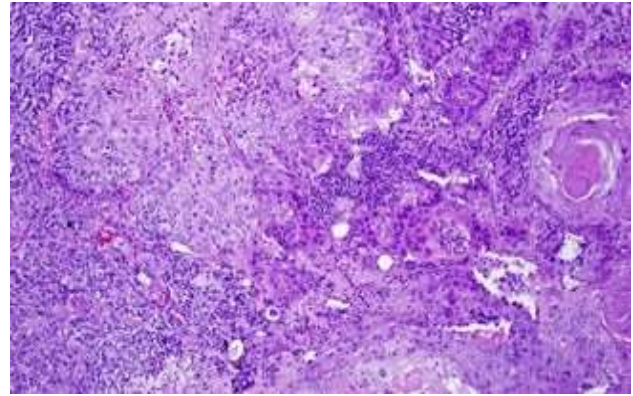


Figure 3: Histopathology image showing small tumour cells arranged in sheets and small nests separated by thin septae with some areas of crushing and moulding of nuclei.

Immunohistochemical study showed tumor cells that expressed diffuse and strong positivity for synaptophysin, CD56 and CK (focal paranuclear dot-like at places) and immunonegative for c-kit, CD3, CD20 and CD10 (Figure 4). The mib-1 labelling index was approximately 50% in areas of highest proliferative activity. The lesion was diagnosed as small cell carcinoma.

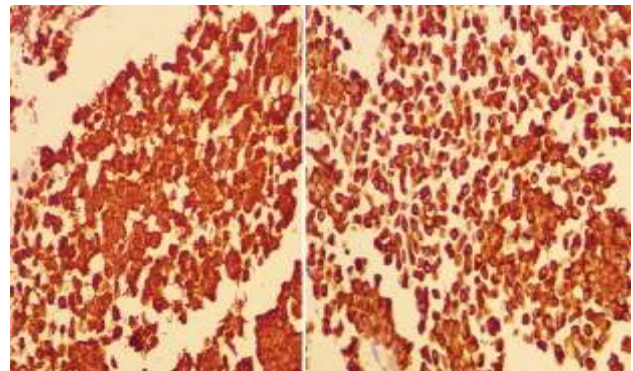


Figure 4: Immunohistochemistry showing tumour positivity to synaptophysin and cytokeratin respectively.

Patient was subjected to radiological investigations to look for distant metastasis which was found to be absent. She was given concurrent chemoradiotherapy. She received 2 cycles of systemic chemotherapy with cisplatin (80 mg/m², day 1) and etoposide (100 mg/m², days 1–3) at 4-week interval and concurrent radiotherapy by conventional fractionation at 2 Gy/fraction/day with a total dose of 66 Gy. Follow up of the patient after nine months did not reveal any loco-regional recurrence or distant metastasis and patient continues to be tumour-free.

DISCUSSION

Small cell carcinoma is an uncommon type of malignant epithelial neuroendocrine neoplasm. It is most commonly of pulmonary origin. The most common extrapulmonary

sites include esophagus, stomach, colon and rectum, gall bladder, head and neck, urinary bladder, prostate, skin and cervix. Extrapulmonary neuroendocrine small cell carcinoma is a relatively rare disease, accounting for 2.5 to 5% of all small cell neuroendocrine carcinomas.⁵ Larynx is one of the most common extrapulmonary sites of small cell carcinoma although it constitutes only 0.5% of laryngeal neoplasms.⁵ The first small cell carcinoma of larynx was reported by Olofsson and van Nostrand in 1972.⁶

According to Ferlito et al only about 180 cases were reported in the literature until 2006 and only a few have been added since then.⁷ The exact incidence of this disease is difficult to interpret as many cases have been described as poorly differentiated squamous cell carcinoma, anaplastic carcinoma, basaloid squamous cell carcinoma and solid variant of adenoid cystic carcinoma.⁴ Small cell carcinoma is characterized by presence of tumour cells having diameter of less than 3 small resting lymphocytes, scant cytoplasm, high cell proliferation (high Ki67) along with frequent necrosis.

Supraglottis is the most common affected site and small cell carcinoma of subglottis is a rare entity. Fewer than 50 cases of subglottic small cell carcinoma have been reported in the literature. Patients are mostly men who are heavy cigarette smokers in the age group of 50-60 years (range 23-91 years).⁷ Presentation is similar to any other laryngeal neoplasm and varies according to the site/extent of disease. Symptoms of subglottic small cell carcinoma include hoarseness, dyspnea and dysphagia. The tumour is known for its aggressive nature as more than 90% of these cases develop metastasis eventually.⁸ Cervical lymph nodes, bone, skin, liver and lung are the most frequent sites of metastasis. Even if metastasis is absent at initial presentation, the presence of micro metastases cannot be ruled out which become clinically evident after a while. Hence the tumour should be considered as a disseminated disease at presentation.⁹ In our report, we present the case of a 45 year old non-smoker female who was diagnosed with subglottic small cell carcinoma. This is an unusual presentation because it presented as an extrapulmonary small cell neuroendocrine tumour in the subglottis in a non-smoker female patient.

Small cell carcinoma of larynx can also present with paraneoplastic syndromes similar to small cell carcinoma of lung. Various paraneoplastic syndromes like syndrome of inappropriate secretion of antidiuretic hormone [SIADH] or Schwartz-Bartter syndrome, myasthenic syndrome of Eaton-Lambert and ectopic adrenocorticotrophic hormone syndrome have been reported in cases of laryngeal small cell carcinomas.¹⁰⁻¹² Our patient did not have any paraneoplastic syndrome on evaluation.

Small cell carcinomas are classified histologically into oat cell, intermediate cell or combined-cell types. In oat cell type, cells are small with hyperchromatic nuclei and sparse

cytoplasm; mitotic activity and cell necrosis are common. Intermediate cell type is characterized by slightly larger cells with more abundant cytoplasm. Combined type is a mixture of small cell carcinoma with another tumor, usually squamous cell carcinoma or adenocarcinoma. Immunohistochemistry is a valuable tool for diagnosing laryngeal small cell carcinoma. These tumors may express positivity for cytokeratin, carcinoembryonic antigen, epithelial membrane antigen, neuron-specific enolase, synaptophysin, CD56, CD57 and various neuropeptides. After diagnosis is confirmed by histopathology, it is also important to look for distant metastasis as most of these tumours eventually develop metastasis.⁸

Concurrent chemoradiotherapy is considered the treatment of choice for laryngeal small cell carcinoma currently.¹ Baugh et al conducted a study in which the various modalities for treating laryngeal small cell carcinomas were compared and they found that combined chemoradiotherapy results in a significantly longer survival rate than with any other treatment modality.¹³ Radiotherapy is often combined with chemotherapeutic agents like cisplatin and etoposide. Radical surgery is reserved only for local relapse with no evidence of metastasis.⁷ Only 7.7% of laryngeal small cell neuroendocrine tumours metastasize to the central nervous system and as a pre terminal event; so prophylactic cranial irradiation is not indicated.¹⁴

Small cell neuroendocrine tumor of larynx has a poor prognosis, similar to that of small cell lung cancer.⁴ In the review by Gnepp et al 73% of patients with this tumor died of disease with widespread metastases with a mean survival time of 9.8 months (range 1-26 months).¹⁵ Soga et al reported a 5 year survival rate of 7.7% in 2004.¹⁶ Survival rate depends significantly on the extent of the disease.¹⁷ Our patient continues to be tumour-free at nine months post therapy. She is currently on follow-up.

CONCLUSION

Small cell neuroendocrine tumour is an unusual neoplasm of larynx which most commonly affects the supraglottis. It is an aggressive neoplasm with a high chance of distant metastasis and is considered as disseminated disease at initial presentation itself. Presentation is similar to other laryngeal neoplasms and may also be associated with various paraneoplastic syndromes. Concurrent chemoradiotherapy is the treatment of choice; surgery is reserved only for relapse cases.

The extent of the disease is the most significant prognostic factor for survival in these cases. Further studies are essential to understand the behavior of this neoplasm in more detail, which may help in improving the prognosis.

Funding: No funding sources

Conflict of interest: None declared

Ethical approval: Not required

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Cite this article as: Sunil KC, Kumar BYP, Hari M, Ali MA, Veenapani MK. Small cell neuroendocrine carcinoma of subglottis: a case report. *Int J Otorhinolaryngol Head Neck Surg* 2021;7:892-5.