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Clinical Record

Extra-pulmonary small cell carcinoma of the neopharynx: case report and review of neopharyngeal tumours after total laryngectomy

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Abstract

Objective: We report the first documented case in the world literature of primary extra-pulmonary small cell carcinoma occurring in the neopharynx following laryngectomy.

Method: We present a case report and a review of the world literature regarding the management of tumours of the neopharynx and extra-pulmonary small cell carcinoma.

Results: The paucity of cases of extra-pulmonary small cell carcinoma has resulted in many departments managing this neoplasm similarly to pulmonary small cell cancer. However, the site of the primary can have an impact on disease survival and treatment options.

Conclusion: Neopharyngeal small cell carcinoma has not previously been reported. It should be managed in the same way as other extra-pulmonary small cell carcinomas occurring within the pharynx or larynx, with combined multi-drug chemotherapy and radiotherapy. Surgery has a limited role due to the aggressiveness of the disease and the high risk of local and distant spread at presentation.

Key words: Laryngectomy; Pharynx Neoplasms; Tumour Metastasis

Introduction

A neopharynx is a surgically reconstructed pharynx. It can be primarily reconstructed from the remnant of pharyngeal mucosa left following laryngectomy. However, if less than half the circumference of the pharynx is available, stricture formation may result. The alternatives are to graft a neopharynx totally or partially using myocutaneous, gastro-omental or jejunal free tissue flaps. These techniques have been used to good effect; however, neopharynges created partially or totally from graft material are associated with higher morbidity and mortality rates.[1–4]

Post-operative dysphagia has been reported in 10–16 per cent of cases following total laryngectomy.[5,6] Some studies have found no association between neopharynx lumen diameter and functionality, whereas others have suggested that a tumour-free lumen of at least 1.5 cm (2.5 cm stretched) is needed to allow for adequate swallowing. Removal of the larynx results in increased resistance to flow through the neopharynx, due to a loss of superior and anterior laryngeal movement that would normally assist in the opening of the upper oesophageal segment. The above factors, combined with increased tortuosity of the pharynx as a result of tracheostomy, can lead to physiological dysphagia. Therefore, in patients with a neopharynx who present with dysphagia, it may be easy to miss benign pathology (such as strictures, pouches, gastroesophageal reflux and fistulae) as well as malignantpathology (either primary, recurrent or a second primary (either synchronous or metachronous)) involving the neopharynx. Gibbons *et al.* reported a 50 per cent detection rate for abnormalities of the neopharynx and oesophagus on barium swallow, in their series of 204 patients following total laryngectomy.[6]

Patients with head or neck cancer are at increased risk of synchronous and metachronous lesions, in comparison with the general population. A high degree of suspicion and low threshold for investigation are imperative for such individuals. Sonographic, radiological and endoscopic methods of screening the neopharynx have been proposed to increase the detection rate of neopharyngeal tumours.

Tumour recurrences have been reported (see Table I) up to 38 per cent.[7,8] All cases in the neopharynx were that of recurrent squamous cell carcinoma and associated factors were; salvage surgery, degree of tumour extension, lymph node infiltration, poor tumour differentiation and transglottic/sub-glottic localisation of the primary tumour.[9] Second primary malignancies are thought to be independent from primary tumour staging and distant and delayed metastases.[11]

By definition, a diagnosis of extra-pulmonary small cell carcinoma requires a histological diagnosis at the primary site, a normal chest radiograph and computed tomography (CT) scan, and normal sputum cytology or negative bronchoscopy.[19]

We present a patient with primary extra-pulmonary small cell carcinoma in the neopharynx, the first reported case of its kind. We also review the literature on the management of neopharyngeal carcinoma, and we discuss the management of extra-pulmonary small cell carcinoma in the neopharynx.

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TABLE I

REPORTED NEOPHARYNX TUMOUR RECURRENCE RATES FOLLOWING TOTAL LARYNGECTOMY

Study	Pts (*n*)	Recurrence (%)
Gibbons *et al.*[6]	73	14
Balfe *et al.*[7]	40	38
Jung *et al.*[8]	36	38
Nikoloau *et al.*[9]	308	30
Yuen *et al.*[10]	292	10

Pts = patients

Case report

An 82-year-old, laryngectomised man presented to the head and neck clinic with dysphagia and loss of weight, four years after laryngectomy surgery and adjuvant radiotherapy.

Pharyngoesophagoscopy under general anaesthetic demonstrated a circumferential lesion confined to the neopharynx, causing partial stenosis. A recurrence of the primary laryngeal poorly differentiated squamous cell carcinoma (T_4 N_0 M_0) was suspected. However, histological analysis of biopsy material revealed a neuroendocrine-type small cell carcinoma (Figure 1) (see Appendix 1 for report). Subsequent CT staging to exclude a lung small cell primary showed evidence of scarring from previous tuberculosis but no primary cancer. Staging also detected liver metastases, which were not biopsied. Computed tomography imaging of the tumour clearly demonstrated the tumour's position in the neopharynx (Figure 2).

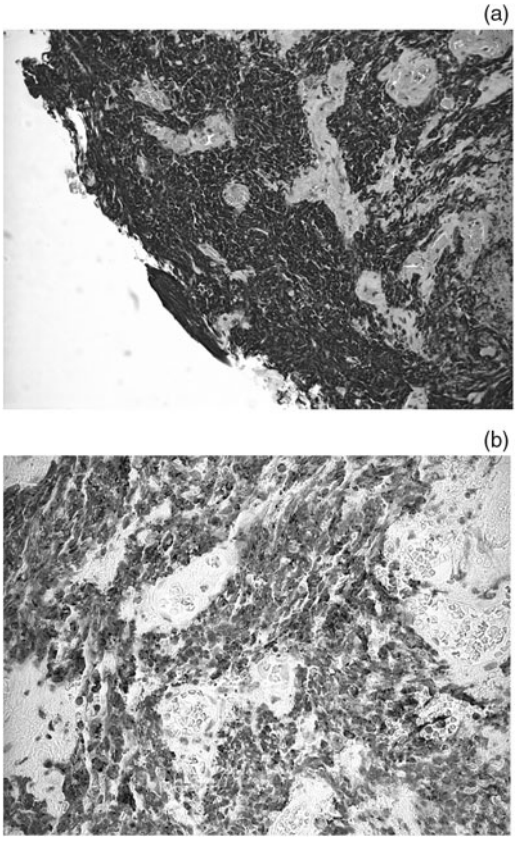

FIG. 1

(a) Photomicrograph of new primary tumour arising in the neopharynx, composed of small, uniform cells with dark, hyperchromatic nuclei and scanty cytoplasm arranged in dense, 'patternless' sheets. Note absence of keratinisation as well as characteristic nuclear 'smudging' (H&E; 1×20). (b) Photomicrograph showing characteristic perinuclear, dot-like immunopositivity for epithelial cell adhesion marker (CAM5.2) seen in small cell carcinoma.

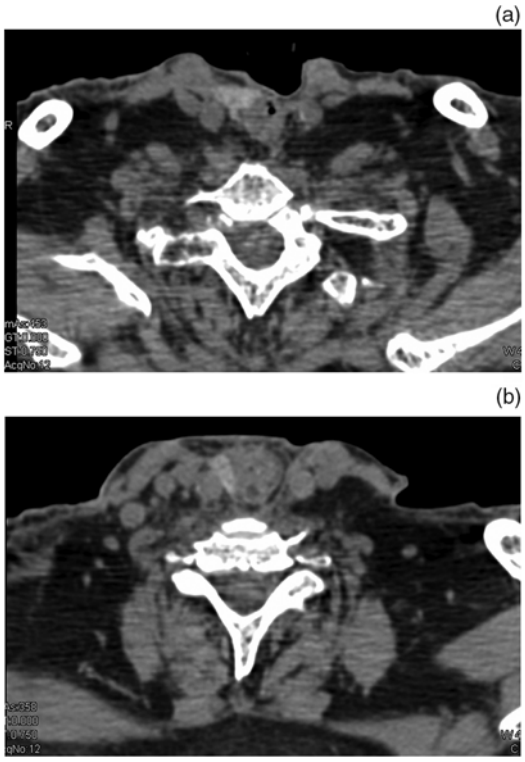

FIG. 2

(a) Axial computed tomography (CT) scan showing tumour at the level of the oropharynx. (b) Axial CT scan demonstrating virtual obstruction of the neopharynx.

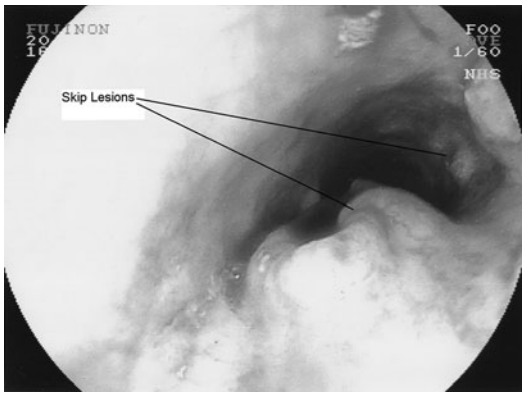

FIG. 3

Endoscopic image demonstrating the primary lesion and skip lesions within the oesophagus.

In the two weeks following diagnosis, a per-cutaneous Gastrostomy feeding tube was inserted. Flexible endoscopy showed extension of the lesion into the oropharynx, and the development of skip lesions along the length of the oesophagus (See Figure 3).

Palliative chemo-radiotherapy was commenced.

Treatment was further complicated by the patient requiring continuous ambulatory peritoneal dialysis for chronic renal failure.

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Discussion

Small cell carcinoma is an aggressive, locally spreading and distant metastasising tumour most commonly associated with the lung (where it accounts for 25 per cent of pulmonary malignancies).[12] It was first documented as a primary lesion outside the lung by Duguid *et al.* in 1930.[13] Since then, the number of documented cases has been limited, with a reported incidence of 0.1–0.4 per cent.[14] Therefore, no valid conclusions can be drawn on prognosis and management. The commonest site of extra-pulmonary small cell carcinoma is the larynx.[12]

From a histogenesis point of view, small cell tumours have embryological links with cells derived from the neural crest, namely the amine precursor uptake and decarboxylation ('APUD') system.[15] This may explain the diversity of sites in which extra-pulmonary small cell carcinomas are found. Small cell carcinomas can also be found in association with squamous cell carcinomas and mucin-producing adenocarcinomas, both within and outside the lung. This has prompted an alternative hypothesis that extra-pulmonary small cell carcinomas derive from pluripotent stem cells.[16] Extra-pulmonary small cell carcinoma sites documented in the literature include: the paranasal sinuses, minor and major salivary glands, hypopharynx, larynx, trachea, thymus, oesophagus, pancreas, stomach, small intestine, colon, rectum, gall bladder, uterine cervix, kidney, urinary bladder, prostate, breast, and skin.[14] Survival rates have been shown to differ depending on the site of disease. Extra-pulmonary small cell carcinoma of the larynx and pharynx has been described as an aggressive disease with a poor prognosis.[17] Two- and five-year survival rates of 16 and 5 per cent, respectively, have been quoted.[18] Surgery is usually not an option because of the high incidence of metastatic disease, so a combination of chemotherapy and radiotherapy is advocated.

Extra-pulmonary small cell carcinoma has often been misdiagnosed as a secondary metastasis from a pulmonary lesion. In recent times, however, it has become recognised as a clinicopathological entity in its own right.

The paucity of such cases has resulted in many departments managing extra-pulmonary small cell carcinoma in a similar way to pulmonary small cell carcinoma. However, Cicin *et al.* have demonstrated a significant difference in the outcomes of patients with extra-pulmonary small cell carcinoma, compared with patients with pulmonary small cell cancers.[13] This may influence the choice of therapy.

- **In patients with a neopharynx, physiological dysphagia following laryngectomy can mask tumour recurrence**
- **Neopharyngeal tumour recurrence is commonly due to squamous cell carcinoma**
- **Primary extra-pulmonary small cell carcinoma of the neopharynx has not previously been reported**
- **Survival rates for extra-pulmonary small cell carcinoma are dependent on the site of disease**
- **Combination chemo-radiotherapy, as opposed to surgery, is advocated for the treatment of extra-pulmonary small cell carcinoma of the pharynx**

Certainly, the histological classification for both extra-pulmonary and pulmonary small cell carcinoma is the same.[19] The diagnosis is based on morphology (i.e. small, uniform cells with hyperchromatic nuclei and sparse cytoplasm arranged in dense, 'patternless' sheets with conspicuous nuclear moulding) and immunohistochemistry (i.e. positive staining for at least one neuroendocrine marker, and perinuclear, dot-like positivity for epithelial markers).

Once the diagnosis is clear, chemotherapy (shown to produce a good response in pulmonary small cell carcinoma patients) should be commenced alongside radiotherapy. Radiotherapy has been found to have disappointing results in treating oesophageal small cell carcinoma, and consequently would not be recommended as the sole treatment modality.[20] Improved outcomes will depend on the development of improved chemotherapy regimens.[17]

The surgical treatment for neopharyngeal recurrence in patients with total laryngectomy is circumferential pharyngectomy with reconstruction or with gastric pull-up for pharyngoesophagectomy. Yuen *et al.* studied a series of 292 laryngectomy patients, including 24 with neopharyngeal recurrence.[10] Of these 24 patients, 10 were deemed suitable for salvage surgery with reconstruction. Recurrent tumour was deemed inoperable if there was fixation onto the skull base or prevertebral muscles, or infraclavicular extension, or if the resultant defect would be unreconstructable. Of the 10 operated patients, one died from a carotid blowout, three died of tumour recurrence, two died of a second primary (surviving 122 and 67 months, variously), two died from apparently unrelated causes (at four and 114 months), and the remaining two were disease-free at five and 145 months. Interestingly, averaging these patients' results revealed a mean survival of 76 months after salvage surgery. Although 40 per cent of the patients were tumour-free at three years, no quality of life measures were used to enable demonstration of true benefit from salvage surgery.

Conclusion

Neopharyngeal small cell carcinoma of the neuroendocrine type has not previously been reported. This neoplasm should be managed in the same way as other extra-pulmonary small cell carcinomas occurring within the pharynx or larynx, with a combination of multi-drug chemotherapy and radiotherapy. Surgery has a limited role due to the aggressiveness of the disease and the high chance of local and distant spread at presentation.

References

1 Stafford ND, Mathews RN. Reconstruction of the pharynx after laryngectomy and partial pharyngectomy. *J Laryngol Otol* 1988;**102**:45–8
2 McConnell FMS, Hester TR, Nahai F, Jurkiewicz MJ, Brown RG. Free jejunal grafts for reconstruction of the pharynx and cervical oesophagus. *Arch Otolaryngol* 1981; **107**:476–81
3 Ariyan S. The pectoralis major myocutaneous flap – a versatile flap for reconstruction in the head and neck. *Plast Reconstr Surg* 1979;**63**:73–81
4 Carlson GW, Thourani VH, Codner MA, Grist WJ. Free gastro-omental flap reconstruction of the complex, irradiated pharyngeal wound. *Head Neck* 1997;**19**:68–71
5 Sullivan PA, Hartig GK. Dysphagia after total laryngectomy. *Curr Opin Otolaryngol Head Neck Surg* 2001;**9**: 139–46
6 Gibbons RG, Halvorsen RA, Foster WL, Warner D, Roberts L, Postlethwait RW *et al.* Esophageal lesions after total laryngectomy. *Am J Radiol* 1985;**144**: 1197–200
7 Balfe DM, Koehler RE, Setzen M, Weymen PJ, Baron RL, Ogura JH. Barium examination of the esophagus after total laryngectomy. *Radiology* 1982;**143**:501–8
8 Jung TTK, Adams GL. Dysphagia in laryngectomized patients. *Otolaryngol Head Neck Surg* 1980;**88**:25–33

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9 Nikolaou A, Markou K, Petridis D, Vlachtsis K, Nalbantian M, Daniilidis L. Factors influencing tumour relapse after total laryngectomy. *B-ENT* 2005;**1**:1–10
10 Yuen APW, Wei WI, Hui Y, Ho WK. Comprehensive analysis of pharyngeal recurrence of laryngeal carcinoma after total laryngectomy. *Am J Otolaryngol* 1996;**17**:380–5
11 Spector GJ, Sessions DG, Haughey BH, Chao CKS, Simpson J, El-Mofty S *et al*. Delayed regional metastases, distant metastases, and second primary malignancies in squamous carcinomas of the larynx and hypopharynx. *Laryngoscope* 2001;**111**:1079–87
12 Ferlito A, Rinaldo A. Primary and secondary small cell neuroendocrine carcinoma of the larynx: a review. *Head Neck* 2008;**30**:518–24
13 Cicin I, Karagol H, Uzunoglu S, Ugun K, Usta U, Kocak Z. Extrapulmonary small cell carcinoma compared with small-cell lung carcinoma. *Cancer* 2007;**110**:1068–76
14 Vrouvas J, Ash DV. Extrapulmonary small cell cancer. *Clin Oncol* 1995;**7**:377–81
15 Gould VE, Memoli V, Chejfec G, Johannessen JV. The APUD cell system and its neoplasms. *Surg Clin North Am* 1979;**59**:93–108
16 Briggs JC, Ibrahim NBN. Oat cell carcinoma of the oesophagus: a clinicopathological study of 23 cases. *Histopathology* 1983;**7**:261–7
17 Weng CT, Chu PY, Liu MT, Chen MK. Small cell carcinoma of the head and neck: a single institution's experience and review of the literature. *J Otolaryngol Head Neck Surg* 2008;**37**:788–93
18 Batsakis JG, El Naggar AK, Luna M. Pathology consultation: neuroendocrine tumours of larynx. *Ann Otol Rhinol Laryngol* 1992;**101**:710–14
19 World Health Organization. The World Health Organization histological typing of lung tumours. *Am J Clin Pathol* 1982;**77**:123–6
20 Medyesy DC, Wolf R, Putnam JB, Ajani JA. Small cell carcinoma of the esophagus. *Cancer* 2000;**88**:262–7

Appendix 1. Neopharynx biopsy report

The biopsy comprises four fragments of completely necrotic tissue and two fragments of squamous mucosa infiltrated by a malignant tumour composed of small, uniform cells with small, hyperchromatic nuclei and little cytoplasm, arranged in dense, patternless sheets, which are focally crushed.

There is conspicuous nuclear moulding. Apoptotic bodies as well as mitotic figures are frequent and there is extensive necrosis.

Immunohistochemistry shows strong and diffuse staining for TTF-1 and synaptophysin. CAM5.2 and MNF116 show perinuclear, dot-like positivity. S100, PGP9.5, NSE, CD56, LCA and chromogranin are negative.

Comment: The immunoprofile is that of a small cell carcinoma of the lung. In the absence of dysplasia in the overlying squamous epithelium, this raises the possibility of a metastasis.

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