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CASE REPORT

Small Cell Neuroendocrine Carcinoma of the Oropharynx Harbouring Oncogenic HPV-Infection

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Abstract Small cell carcinoma/neuroendocrine carcinoma (SCNEC) of the oropharynx is uncommon. Recently, an association has been reported between oropharyngeal SCNEC and high-risk human papillomavirus (HPV) infection. While HPV infection confers a better prognosis for oropharyngeal squamous cell carcinoma, HPV infection does not appear to influence the biological behaviour of SCNECs, which are generally associated with poor clinical outcomes. We document two cases of SCNEC arising in the oropharynx with evidence of high-risk HPV infection. The cases highlight the expanding range of malignant oropharyngeal neoplasms that harbour oncogenic HPV infection and support the concept that, irrespective of HPV infection, neuroendocrine differentiation portends a poor prognosis.

Keywords Neuroendocrine carcinoma · Small cell carcinoma · Human papillomavirus (HPV) · Oropharynx

Introduction

Cells of the diffuse neuroendocrine system comprise diverse populations in the head and neck region. Their biological roles are poorly characterised [1]. Malignant head and neck tumours with a neuroendocrine phenotype are uncommon. Most primary neuroendocrine carcinomas (NECs) in the head and neck region arise in well-documented subsites (e.g. thyroid, larynx, and salivary glands) [2]. The possibility of metastasis from a distant primary tumour (most commonly pulmonary small cell carcinoma) should be considered [2, 3]. The literature contains a relatively small number of articles reporting NECs arising of the oral cavity/oropharynx [1, 3–15]. Exposure to tobacco and alcohol are implicated in the aetiology of NECs arising in the oral cavity [3, 11]. These carcinogens are also significant risk factors for the development of squamous cell carcinomas (SCCs). Over the past decade it has emerged that human papillomavirus (HPV) infection is significant in the aetiology of a subset of oropharyngeal SCCs [2, 16, 17]. This subset is associated with a good prognosis (3-year survival rates of up to 80 %) [18]. HPV infection has been reported in histological variants of SCC: adenosquamous carcinoma [19]; basaloid SCC [20]; papillary SCC [21]; and lymphoepithelial carcinoma [22].

Oncogenic HPV has also been described in 13 cases of oropharyngeal small cell neuroendocrine carcinoma (SCNEC) [6, 10, 11]. In contrast to the good prognosis reported for HPV-positive SCC, there is evidence to suggest that these cases pursue an aggressive clinical course [10, 11]. The expanding range of malignant oropharyngeal neoplasms associated with HPV infection raises questions as to the precise role of HPV infection in the formation of tumours with diverse phenotypes and clinical outcomes.

We document the clinical course of two patients with oropharyngeal HPV-related SCNEC.

Case Histories

The patients' details, immunohistochemical profiles and HPV status are summarised in Table 1.

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Table 1 Summary of the demographic details, immunohistochemistry profiles, and results of HPV tests for Cases 1 and 2

	Case 1	Case 2
Year of diagnosis	2011	2006
Age at diagnosis (years)	64	59
Sex	Female	Male
Tobacco	5 cigarettes/day	Unknown
dPAS	Negative	Negative
AE1/AE3	Weak dot-like positivity	Membranous and dot-like positivity
CK5/6	Negative	Negative
CK7	Patchy, weak dot-like positivity	Membranous and dot-like positivity
CK20	Negative	Negative
Synaptophysin	Strongly positive	Negative
Chromogranin	Positive	Granular cytoplasmic positivity
CD56	Strongly positive	Negative
PGP9.5	Scattered weakly positive cells	Negative
TTF-1	Patchy, weak nuclear positivity	Negative
CEA	Negative	Negative
Calcitonin	Negative	Negative
Ki67	100 %	70 %
p16	Strong cytoplasmic and nuclear positivity	Strong cytoplasmic and nuclear positivity
HR-HPV-ISH	Punctate nuclear positivity	Punctate nuclear positivity
Cobas HPV test	HPV18	HPV16

Case 1

The patient presented with a two-month history of sore throat. Clinical examination revealed a polypoid mass in the left oropharynx that extended from the upper pole of the left tonsillar fossa to the uvula. There was also an enlarged lymph node at left level II. Clinical staging by CT confirmed a broad-based polypoidal mass in the left oropharynx (Fig. 1) with a maximum dimension of 18 mm and a lymph node metastasis at level II with a maximum dimension of 16 mm. There were no other lesions in the brain, head and neck, chest or abdomen (cT1N1M0, clinical Stage III). An incisional biopsy of the mass showed a malignant neoplasm formed of nests, islands and lobules of small to medium-sized basaloid cells. The majority of the malignant cells exhibited nuclei with a smooth chromatin pattern with indistinct nucleoli. The malignant cells showed scanty cytoplasm and indistinct cell borders. Mitotic figures and apoptotic bodies were readily identifiable. Several of the larger tumour islands showed peripheral palisading and comedonecrosis (Fig. 2a). The histological features were consistent with SCNEC. The immunohistochemical profile of the tumour is described in Table 1 and shown in Fig. 2b–d. The malignant cells showed strong nuclear and cytoplasmic expression of p16 by immunohistochemistry (CINtec Histology, Roche mtm laboratories AG, Germany) (Fig. 2e). There was evidence of high-risk HPV DNA by ISH (Inform HPV III Family 16 Probe B, Ventana Medical Systems Inc., USA) (Fig. 2f) and a Cobas® HPV test (Roche Molecular Systems Inc. USA) demonstrated HPV 18 infection. The patient was treated with sequential chemoradiotherapy. Following induction with 6 cycles of carboplatin and etoposide, she underwent radiotherapy to the left tonsil and neck (65 Gy in 30 fractions). Although surveillance CT imaging at 4 months showed a size reduction in both the oropharyngeal mass and left level II lymph node, a follow up PET scan 12 months later revealed metastases to the lungs and liver. The patient received palliative second-line chemotherapy with Topotecan, but the disease continued to progress and she died of disease (disease-specific survival 15 months).

Case 2

The patient presented with a left sided neck swelling. Fine needle aspiration cytology of a clinically palpable left level II lymph node showed features consistent with SCNEC. Clinical workup and staging investigations did not reveal any obvious primary disease. The working diagnosis was SCNEC of uncertain origin. The patient received three cycles of carboplatin and etoposide chemotherapy. The neck disease did not respond to the treatment and in view of chemotherapy refractory disease, he underwent laryngoscopy, pharyngoscopy, biopsies of left tongue base and

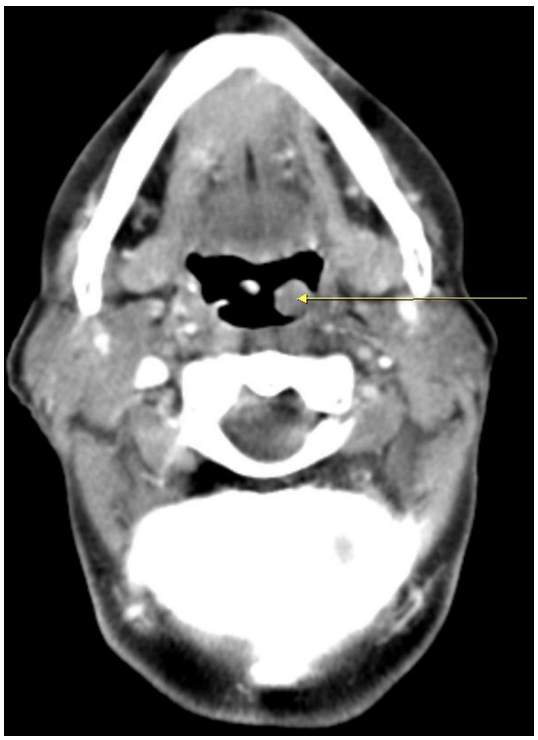

Fig. 1 Axial CT scan of Case 1 showing a polypoid lesion arising from the *left* palatine tonsil (*arrowed*)

left tonsillectomy. Histology from the lower pole of the left tonsil showed SCNEC. The morphological features were similar to those described for Case 1. The tumour comprised lobules and nests of small to medium-sized cells with scanty cytoplasm and ill-defined cell borders. Nuclei were hyperchromatic, with a slightly granular chromatin pattern and indistinct nucleoli. There was prominent nuclear moulding. Mitotic figures were readily identifiable. The immunohistochemical profile is outlined in Table 1. The malignant cells showed membranous and dot-like expression of pan-cytokeratin and cytokeratin 7 (CK7). Cytokeratins 5/6 (CK5/6) and 20 (CK20) were negative. There was granular expression of chromogranin, however, synaptophysin and CD56 were negative. The malignant cells showed strong nuclear and cytoplasmic expression of p16. There was evidence of high-risk HPV DNA by ISH and Cobas® HPV test demonstrated HPV 16 infection. The patient underwent resection of the left tonsil and tongue base, and a bilateral neck dissection. Excision of the primary tumour was incomplete and metastatic carcinoma was identified in 6 of 43 lymph nodes with extracapsular spread of disease. Post operative staging was pT3 pN2b M0 (Stage IVA disease). The patient received adjuvant radiotherapy (63 Gy in 30 fractions). The patient subsequently developed biopsy proven liver metastases 25 months after initial presentation and died of disease (disease-specific survival 26 months).

Discussion

Tumours showing neuroendocrine differentiation occur most commonly in the lung and gastrointestinal tract [23]. Most NECs in the head and neck region arise in the either

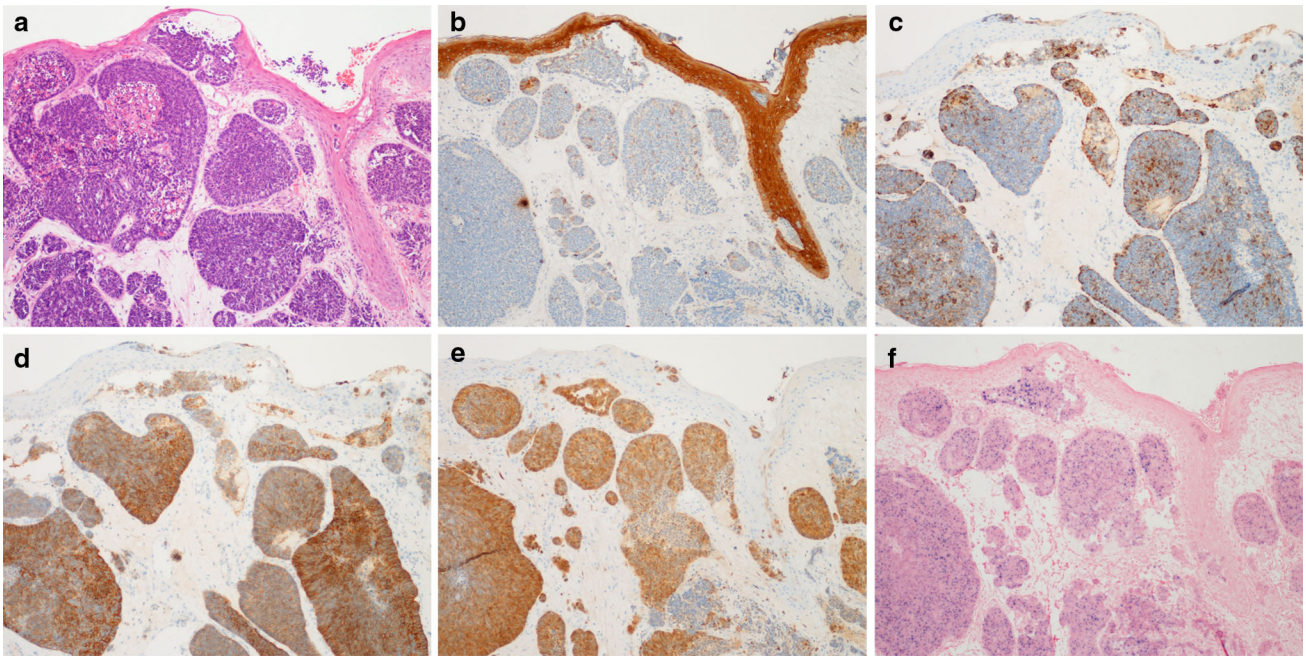

Fig. 2 Photomicrographs of the biopsy from Case 1. **a** H and E, **b** AE1/AE3, **c** chromogranin, **d** CD56, **e** p16, **f** high-risk HPV ISH (magnification ×100 for all images)

Table 2 A classification system for primary oral/oropharyngeal NECs, adapted from Mahomed [1]

Small cell type NEC (small tumour cells)	Non-small cell type NEC (medium to large tumour cells)
Subtypes	Subtypes
Merkel cell carcinoma	Typical carcinoid (well diff. NEC)
Small cell/high-grade carcinoma (pulmonary type)	Atypical carcinoid (moderately diff. NEC)
Primary	Large cell/poorly diff. NEC
Metastatic	

the thyroid or larynx [24]. Our search of the literature identified a limited number of articles documenting NECs of the oral cavity/oropharynx (including both primary and metastatic tumours). These include single case reports [4–9], small case series [10–13], and review articles [1, 3, 14, 15].

The small number of reported cases has precluded definitive classification of primary oral/oropharyngeal NECs. A review by Mahomed [1] separates these tumours into two categories, either small cell or non-small cell types, using a diagnostic algorithm with morphological and immunohistochemical parameters (Table 2). A recent comparative study by Lewis et al. [3] further delineated the classification of small cell type NECs into two subcategories: Merkel cell carcinoma (MCC) and small cell (high-grade) carcinoma (SCNEC). The current cases are both consistent with SCNEC as described in these papers.

Oncogenic HPV infection, particularly HPV16, is significant in the aetiology of a subset of oropharyngeal SCCs [16, 25]. Recognition of the favourable outcomes associated with this subset has led to the routine use of HPV tests for diagnosis, prognostication and clinical trials registration [17, 18, 26, 27]. In recent years, the range of malignant oropharyngeal neoplasms associated with HPV infection has expanded to include several histological variants of SCC [19–21].

The aetiopathogenesis of NECs is poorly understood. MCCs arising at cutaneous sites have a predilection for sun-exposed sites, suggesting UV-light is a risk factor [1]. Merkel cell polyomavirus has also been in detected in a substantial proportion of cutaneous MCCs, but not in those at mucosal sites [3]. Alcohol and tobacco exposure have been implicated in the aetiology of SCNECs arising in the oral cavity/oropharynx. SCNECs arising in the female genital tract have a well-recognised association with HPV infection [28–30]. Recently, HPV-related SCNECs have also been reported in the sino-nasal tract [31] and the lower gastro-intestinal tract [32].

HPV-infection has also been implicated in the aetiology of oropharyngeal SCNECs. Our cases add to two recent series and a case report which, combined, document 18 primary oropharyngeal SCNECs. The patients were generally in late middle-age (range 35–83 years of age). Tobacco exposure was implicated as a risk factor in the majority (12 cases) as well as high-risk HPV infection (13 cases) [6, 10, 11]. The coincidence of these major risk factors raises questions as to their relative contribution to the development of SCNEC in the oropharynx. The subgroup of HPV-positive cases had a male preponderance (male:female ratio = 11:2). Our cases did not show an association between oropharyngeal SCNEC and conventional SCC, however, tumours with concurrent features have been reported in 6 cases [10, 11]. Overall, the outcome data for these patients suggest that neuroendocrine differentiation signals an aggressive phenotype irrespective of HPV-positivity. Aggressive behaviour of HPV-positive SCNECs has also been documented in the female genital tract [25]. However, there is some evidence to suggest that HPV-positivity may confer a prognostic advantage in SCNEC of the oropharynx. In the series published by Bishop and Westra [10], two of the five cases with HPV-positive SCNEC showed a complete response to therapy (time to last follow-up 5 and 20 months). By contrast, all four cases with HPV-negative SCNEC developed distant metastases and died with the disease. At the present time, reliable prognostication is precluded by the small number of reported cases, and the variability of follow-up data available. However, on balance, the present cases suggest that outcomes for oropharyngeal HPV-positive SCNEC are poor in comparison to HPV-positive SCC at the same site.

Conclusion

We document two cases of SCNEC arising in the oropharynx with evidence of high-risk HPV infection. These cases highlight the expanding range of malignant oropharyngeal neoplasms that are associated with the presence of high-risk HPV. They support the concept that, irrespective of HPV infection, neuroendocrine differentiation generally portends a poor prognosis relative to HPV related squamous cell carcinomas arising at this site.

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