Tonsillar Small Cell Carcinoma: Potential Contribution of Human Papillomavirus

Roger A. Fecher
Brittany A. Leader
Yash Patil
Randall Butler

Corresponding Author: Randall Butler, e-mail: randall.t.butler@gmail.com

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Patient: Female, 64
Final Diagnosis: Small cell carcinoma of the tonsil
Symptoms: Sore throat
Medication: —
Clinical Procedure: —
Specialty: Oncology

Objective: Unknown ethiology

Background: Extrapulmonary small cell carcinoma (SmCC) is a relatively rare clinical entity constituting only 2.5–5% of SmCCs. Recently, evidence has emerged that high-risk types of human papillomavirus (HPV) might play an etiologic role in oropharyngeal SmCC, similar to squamous cell carcinoma.

Case Report: Here, we present a case of tonsillar SmCC that presented as combined SmCC-squamous cell carcinoma in a cervical lymph node, raising the possibility that the SmCC-component represents disease progression.

Conclusions: This case lends further support to the importance of HPV in the development of oropharyngeal SmCC and suggests a mechanism of disease progression.

MeSH Keywords: Carcinoma, Small Cell • Disease Progression • Papillomavirus Infections

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**Background**

Over the past decade, high-risk human papillomavirus (HPV) has been recognized as a primary etiologic agent of oropharyngeal squamous cell carcinoma in addition to tobacco use and alcohol abuse [1]. Human papillomavirus-associated squamous cell carcinoma is a relatively common head and neck cancer, and the presence of HPV is associated with a good prognosis [1].

Although the etiology of oropharyngeal small cell carcinoma (SmCC) is unknown, several groups have reported cases associated with HPV infection [2–5]. While oropharyngeal SmCC is a relatively rare tumor, 14 of 15 recently reported cases were positive for both p16 and HPV [2–5]. Unfortunately, HPV infection does not improve the prognosis of oropharyngeal SmCC, which is associated with early lymph node and systemic metastases [2,4].

We present a case of combined SmCC-squamous cell carcinoma in a cervical lymph node with pure SmCC in the tonsil. HPV infection of the tonsillar component was confirmed with p16 staining, raising the possibility that SmCC morphology represents a form of disease progression.

**Case Report**

A 64-year-old white woman presented to her primary care physician with right neck swelling of 3 months’ duration and a sore throat of 2 months’ duration. She had no history of smoking and had scant alcohol consumption. Her medical history was significant for rheumatoid arthritis, type 2 diabetes mellitus, essential hypertension, coronary artery disease, chronic obstructive pulmonary disease, and hypothyroidism. Her chronic conditions were well controlled and stable. Notable surgical history included a right lung lobectomy for benign disease 3 years prior.

She initially received 2 courses of amoxicillin, but both failed to yield improvement. A CT of the neck revealed a conglomerate of enlarged right-sided level II lymph nodes (Figure 1). Lymph node excisional biopsy identified a neoplasm, in which the majority of cells were SmCC, with a minor component of squamous carcinoma (Figure 2A–2E). The squamous cell component consisted of irregular islands of cells with marked pleomorphism surrounding central regions of obvious keratinization. The SmCC component consisted of sheets of cells with high nuclear-to-cytoplasmic ratios, brisk mitotic rate, and areas of necrosis. The differential diagnosis for the small cell component included metastasis of a Merkel cell carcinoma and lymphoma. Immunohistochemical stains demonstrated that the squamous carcinoma component was positive for cytokeratin 5/6 and p40, while the SmCC component was positive for synaptophysin. Merkel cell and lymphoma were eliminated from the differential diagnosis with positive TTF1 (not shown) and cytokeratin staining, respectively.

A staging PET/CT was obtained. The right tonsillar pillar/tongue base was identified as the likely site of the primary tumor, and hypermetabolic right level V lymph nodes were identified, consistent with metastatic adenopathy. The remainder of the neck, chest, abdomen, and pelvis were negative. A right tonsil and base of tongue biopsy revealed pure SmCC (Figure 2F–2H). By immunohistochemistry, the neoplastic cells were diffusely positive for synaptophysin and p16. The patient was diagnosed with SmCC of the tonsil with metastatic disease to multiple lymph nodes, consistent with clinical stage IVA, TXN2b.

The patient was started on neoadjuvant therapy and received 4 cycles of carboplatin and etoposide, as well as radiation therapy to the neck, but her course was interrupted due to sepsis and pancytopenia. Unfortunately, treatment failed to halt the progression of her disease. Follow-up PET/CT at 6 months revealed metastases in right neck lymph nodes at levels II and III and osseous lesions in the left glenoid region, L5 vertebra, left iliac bone, and left subtrochanteric hip, with resolution of the right tonsillar nodule. She was therefore started on pembrolizumab as well as additional radiation therapy for the bone metastases.

**Discussion**

The classic etiologic agents of head-and-neck squamous carcinomas are tobacco and alcohol [1]. Evidence accumulated over
the past 15 years has demonstrated that high-risk HPV is an additional primary causative agent among the subset of tumors that arise in the oropharynx [6]. HPV-positive tumors are now thought to account for 5–20% of all squamous cell carcinomas of the head and neck, with most arising in the oropharynx [7]. While the contribution of HPV to other oropharyngeal cancers is still unclear, multiple studies have identified HPV in pure SmCC of the oropharynx [2–5]. Even though oropharyngeal SmCC is uncommon, HPV was detected in nearly all recently reported cases; specifically, the vast majority overexpressed the surrogate marker p16 on immunohistochemistry and harbored high-risk HPV on confirmatory testing (in situ hybridization and/or polymerase chain reaction) [2–5].

Genetic and phenotypic analyses to elucidate the development of head-and-neck combined SmCC and squamous cell carcinoma have not been reported; however, combined SmCCs in the lung have been investigated. One study performed immunohistochemical and loss of heterozygosity (LOH) analysis in 7 lung neoplasms in which SmCC was combined with a non-small cell component (adenocarcinoma, squamous carcinoma, or large cell neuroendocrine carcinoma) and found that the 2 components were immunophenotypically similar [8]. The morphologically distinct components also shared LOH on multiple chromosome arms, with no discordant LOH observed. This analysis suggests that SmCC and non-small cell components are closely related despite their distinct histologic appearance.

The development of morphologically heterogeneous tumors with underlying genetic similarities supports the notion of a common precursor cell, or cancer stem cell [9,10]. Such neoplasms might arise from cancer stem cells with concurrent or sequential differentiation into morphologically distinct components [11]. While the tonsillar biopsy in our case demonstrated pure SmCC morphology, the excised cervical metastases exhibited both squamous carcinoma and SmCC. These observations, in conjunction with the established etiologic role of HPV in oropharyngeal squamous carcinomas, the overexpression of p16 in the tonsillar primary tumor in this case, and the findings of others, raise the possibility that the SmCC component represents tumor dedifferentiation/tumor progression [2–5].

Squamous cell carcinomas that are positive for HPV are associated with a better prognosis and increased survival compared to their HPV-negative counterparts [6]. SmCC, in contrast, carries a poor prognosis, with proclivity for locally aggressive disease and regional and distant metastases [2,4,11]. The SmCC component of this patient’s disease may represent disease progression; the rapid development of systemic metastases despite combined chemoradiotherapy bolsters this hypothesis.

Head and neck SmCC is typically aggressive, with early metastases to regional lymph nodes and systemic sites. This has led investigators to propose recognition of SmCC as a systemic disease from the onset, with corresponding systemic therapy [11,12]. General opinion favors combination therapy with
systemic chemotherapy and radiotherapy to treat SmCC of the head and neck, with potential surgical resection for those with early local disease [11,13].

Conclusions

We presented a case of combined SmCC-squamous carcinoma within a cervical lymph node, which suggests SmCC might derive from preexisting squamous carcinoma as a form of tumor dedifferentiation, with attendant poor clinical outcomes. Larger case series and genetic analyses may be of value in confirming this hypothesis and developing effective therapeutic strategies.

Conflicts of interest

None.

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