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CASE REPORT

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Combined large cell neuroendocrine carcinoma and squamous cell carcinoma of the oropharynx: A collision course of tumors

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Abstract

Combined large cell neuroendocrine carcinoma (LCNEC) and squamous cell carcinoma (SCC) of the H&N are exceptionally rare. We present the case of combined p16 negative SCC and LCNEC of the oropharynx treated with combination chemotherapy. This is the third reported case of combined neuroendocrine carcinoma and SCC of the oropharynx.

KEYWORDS

carcinoma, large cell, carcinoma, squamous cell, head and neck neoplasms, lung neoplasms, otolaryngology

1 | INTRODUCTION

Despite an expansive knowledge and experience with the treatment of squamous cell carcinoma (SCC) of the head and neck (H&N), large cell neuroendocrine carcinoma (LCNEC) remains exceedingly uncommon and has rarely been reported in the otolaryngology literature.[1–7] Classically, LCNEC has been established as a well-known pulmonary malignancy that is less commonly reported throughout the gastrointestinal and genitourinary tracts, thymus, salivary glands, larynx, oral cavity, and pharynx,[1,6–8] but most inquiries of LCNEC in the H&N are limited to case reports and series. As a result, most prognostic estimates are based on LCNEC of the lung, with few investigations detailing survival rates, optimal treatment paradigms, and patient outcomes in the H&N.[9–12] Treatment of these tumors remains controversial and may involve a combination of early surgical resection, chemotherapy, or radiotherapy, though there is no accepted standardized treatment and depends on a multitude of concurrent

factors such as primary tumor site, involvement of surrounding anatomical structures, and institutional treatment capabilities.[12]

In contrast to LCNEC, SCC is the most common H&N cancer and has well-established prognostic indicators and treatment regimens. The complexity of care for patients with either of these tumors can be compounded by the occurrence of combined primary tumors with neuroendocrine and squamous cell elements.[8,13–16] These combined tumors, or "collision tumors," as they are sometimes called, present a unique challenge for care teams due to their uncertain prognosis and treatment. Literature review of combined neuroendocrine carcinoma (NEC) and SCC revealed few reported cases in the H&N, with the predominant location being in the larynx, while the oral cavity and nasal cavity were less common.[17] The oropharynx was the least common site with two previously reported cases of oropharyngeal combined NEC and SCC.[16,18] Herein, we present a rare case of combined LCNEC and SCC of the posterior oropharyngeal wall, its pathological description and treatment course.

2 | CASE REPORT

A 50-year-old female inmate presented to the ENT clinic with a one-month history of enlarging right neck mass. She was unsuccessfully treated for presumed infection by her primary care provider with a course of antibiotics before evaluation. Although she denied any weight loss, fevers, chills, or night sweats, she endorsed significant odynophagia and worsening foreign body sensation of the throat. Her pertinent medical history included hypertension and hyperlipidemia. She had a 20 pack-year history of cigarette smoking but denied alcohol consumption. Physical examination revealed a firm right level II/III neck mass without any tenderness, drainage of fluid, or overlying skin changes. No discrete oropharyngeal masses were seen on flexible nasolaryngoscopy; however, the right tonsil and posterior tonsillar pillar were firm to palpation. CT neck with contrast was next obtained, which revealed an endophytic 2.8 cm enhancing soft tissue lesion of the right tonsil with an adjacent fluid collection (Figure 1). An additional ipsilateral right neck nodal conglomerate was also seen, which was concerning for metastasis. Fine needle aspiration of the right neck mass was obtained, which revealed otherwise unspecified poorly differentiated carcinoma, which was p40 negative with patchy CD56 positivity.

The decision was made to proceed with direct laryngoscopy and biopsy. Intraoperatively, a firm submucosal lesion of the right tonsil was found, along with an additional mobile mass of the posterior pharyngeal wall. Deep biopsies were taken of both the right tonsil and posterior pharyngeal wall mass. The microscopic findings of the tumor showed two components clearly distinguished by morphology and immunohistochemistry (Figure 2). Microscopy using hematoxylin and eosin (H&E) showed one component of the tumor with a diffuse nested growth pattern with palisading at the periphery of the nests and central necrosis. These tumor cells were polygonal, with large, hyperchromatic nuclei and moderate cytoplasm, and small nucleoli. There were numerous mitotic figures. This component was positive for CD56 and negative for p40 and CK5/6. Synaptophysin and chromogranin were negative. A second component of the tumor consisted of large, atypical, pleomorphic non-keratinizing squamous cells with focal intracellular bridging, occasional prominent nucleoli, and positive immunohistochemical staining for p40 and CK5/6. The entire biopsy specimen was negative for p16, and Epstein–Barr encoding region (EBER)

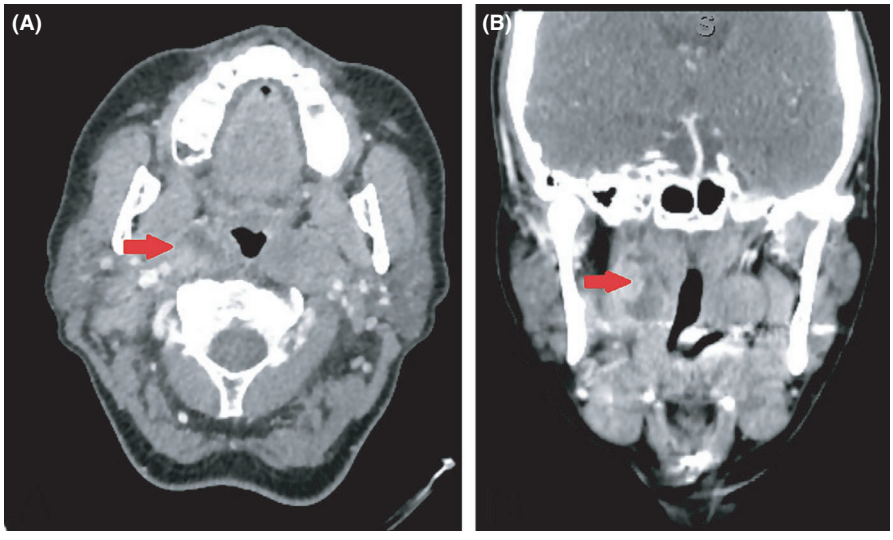


FIGURE 1 Contrast-enhanced CT scan of the neck (A: axial view; B: coronal view) depicting right tonsillar mass with an associated 2.8 cm fluid collection (red arrow). Additionally, a right level II/III necrotic nodal conglomerate measuring up to 5.4 cm was noted

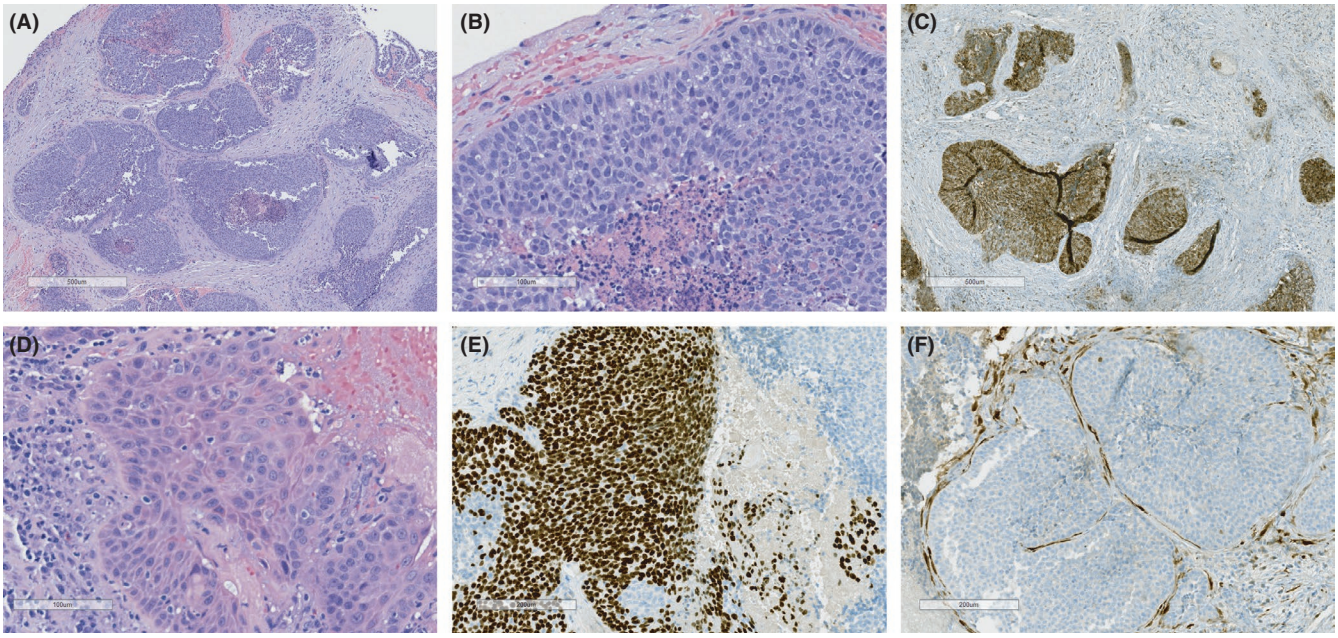
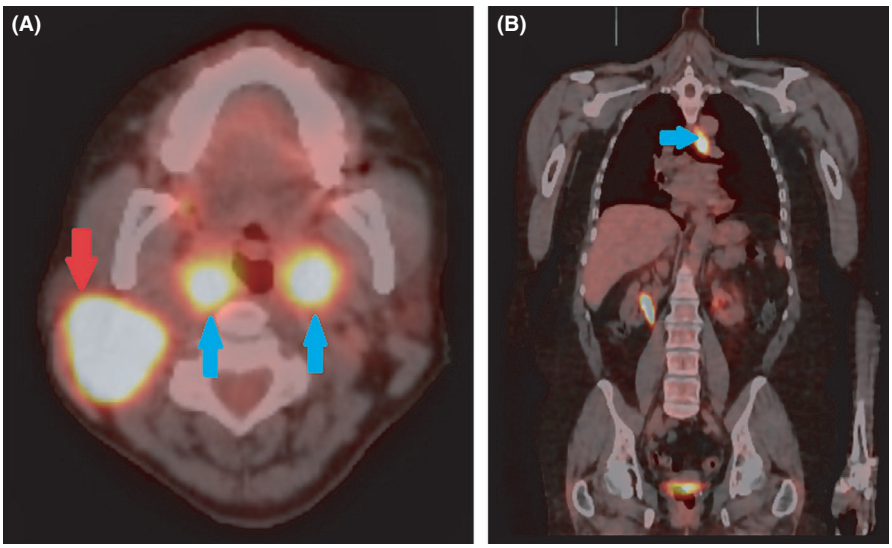


FIGURE 2 Histological findings from combined large cell neuroendocrine and squamous cell carcinoma biopsy: A portion of the biopsy shows tumor cells in a nested growth pattern with necrosis, (A) H&E x40, and is composed of palisading, medium-large atypical tumor cells with a hyperchromatic large nuclei and small nucleoli, H&E (B) x200. On immunohistochemical staining, these nested tumor cells are positive for CD56 (C). A second portion of the tumor is composed of atypical, pleomorphic squamous cells (D) H&E x200, and Immunohistochemical staining are positive for p40 (E). The entire biopsy was negative for p16 (F)

FIGURE 3 (A) PET-CT scan revealed increased FDG uptake of the bilateral palatine tonsils (blue arrows) (SUV 21.8 on the right and 19.5 on the left). In addition, centrally necrotic lymph node conglomerate was again noted in right level II/III neck (red arrow). (B) Increased FDG uptake was avidly seen in the left paratracheal and subaortic lymph nodes, highly suspicious for metastatic carcinoma (blue arrow)



in situ hybridization for Epstein–Barr virus was negative. These findings were consistent with a pathologic diagnosis of combined squamous cell carcinoma and large cell neuroendocrine carcinoma. There was no evidence of carcinoma in either the right or left tonsils.

PET scan was then obtained and showed increased FDG uptake in the bilateral tonsils, necrotic right level II/III lymph nodes, and lower paratracheal lymph nodes suspicious for metastatic carcinoma (Figure 3). Per recommendations of the Head and Neck Tumor Board (HNTB), the patient underwent endobronchial ultrasound (EBUS)-guided fine needle aspiration (FNA) of these nodes (Figure 4). Similar sheets of malignant cells to the oropharyngeal wall biopsy were noted, with high nuclear-to-cytoplasmic ratio, large, rounded nuclei with irregular nuclear borders and occasional enlarged nucleoli. Numerous apoptotic bodies and mitoses were seen. The immunohistochemical findings of these cells were diffusely positive for CD56 and rare cells positive for synaptophysin and chromogranin. These tumor cells were negative for p40, TTF-1 and Napsin A. The final pathologic diagnosis was high-grade, large cell neuroendocrine

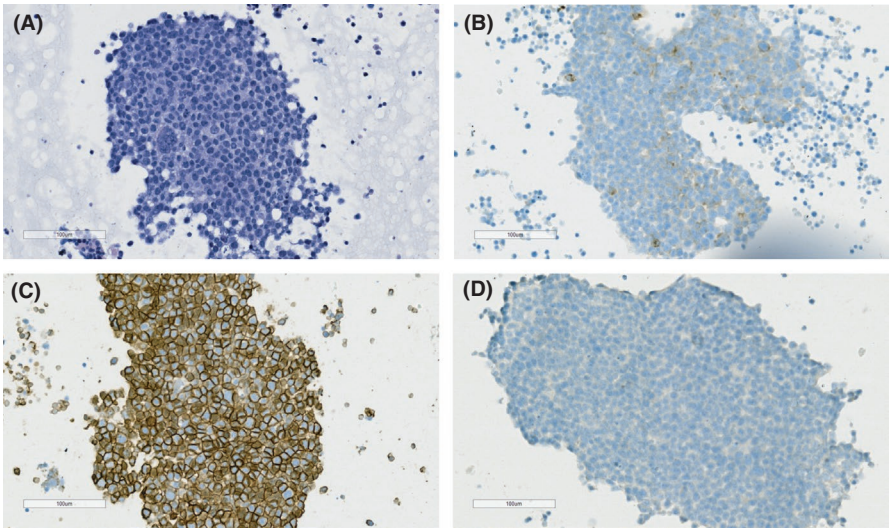


FIGURE 4 Endobronchial ultrasound guided FNA cell block showing high-grade large-cell neuroendocrine carcinoma: (A) These cells are composed of medium-large atypical, pleomorphic cells with large, hyperchromatic nuclei and small nucleoli, H&E x200. Immunohistochemical staining shows (B) rare positive cells for synaptophysin, (C) strongly positive for CD56, and (D) negative for p40

carcinoma. A summary of this patient's histopathologic findings can be seen in Table 1.

Per the decision of the HNTB, the patient proceeded with chemotherapy regimen of carboplatin, etoposide, and atezolizumab. After two cycles of treatment curtailed due to neutropenia, clinical response was excellent with significant decrease in size of neck disease and post-treatment imaging pending. She was subsequently discharged from correctional care, and she continues her cancer treatment in the free world.

3 | DISCUSSION

Although rare in the H&N, neuroendocrine carcinomas (NECs) are described as a heterogeneous group of neoplasms subdivided by the 2017 WHO Classification of Head & Neck Tumors into well-differentiated NEC, moderately-differentiated NEC, and poorly differentiated NEC, which are further divided into small cell and large cell types.[19] This classification scheme offers a useful separation of tumor grades, with poorly differentiated NEC representing the highest grade of tumor. An additional update to the 2017 classification system was that the terms "carcinoid" and "atypical carcinoid" are no longer preferred, shifting the focus to the new naming convention. This represented a generally well-received change that had been pleaded for by authors in previous years.[10,20]

LCNEC was first described in the lungs by Travis et al. in 1991.[21] The diagnosis is based on high-grade features and requires the presence of both neuroendocrine morphologic features (organoid nests, trabeculae, rosettes, and/or peripheral palisading) and immunohistochemical evidence of neuroendocrine differentiation (i.e., immunostaining with synaptophysin, chromogranin, and/or CD56). Most tumors express two or three of these three neuroendocrine markers, and the staining is typically diffuse in at least one of them. However, when the morphology is typical for a LCNEC, it is enough to find any extent of expression of just one neuroendocrine marker to support the diagnosis.[22] The morphologic features of LCNEC may overlap with those of non-keratinizing squamous cell carcinomas. Both tumors may display a basophilic appearance with a high nuclear-to-cytoplasmic ratio, high mitotic rate, peripheral palisading, and necrosis. However, SCC usually demonstrates oval nuclei with finely dispersed chromatin and sheet-like growth, while LCNEC shows more trabecular or nested growth and coarse chromatin. For a definitive distinction, immunohistochemical stains should be used. As in our case, SCC should be strong and diffusely positive for p40 (or p63) and CK5/6 and negative for neuroendocrine markers, while LCNEC is negative for p63 and CK5/6, and it is positive for at least one neuroendocrine marker.

Cases of combined NEC are extremely rare, especially in the oropharynx. To the best of our knowledge, only two cases in the oropharynx have been previously reported, one case in the tonsil and another unspecified advanced oropharyngeal tumor.[16,18] In the case presented here, since LCNEC with similar morphology was seen in both the lungs and in the oropharynx, it may suggest that this represented a primary lung tumor with metastasis to the posterior oropharyngeal wall. However, since SCC was not found in the paratracheal lymph nodes, it is also possible that a primary LCNEC of the lung metastasized to the oropharynx and collided with a background of primary oropharyngeal SCC. Finally, the possibility of a primary oropharyngeal combined tumor with metastasis to the lung must be considered, but this seems less likely given that squamous cells were not seen in the paratracheal lymph node specimen. The lung is known to be the most common site of distant metastasis

TABLE 1 Summary of Histopathologic Findings: In this patient, malignant cells were found in the right neck, posterior pharyngeal wall, and paratracheal lymph nodes. The histopathologic findings are summarized

Summary of patient histopathologic findings				
Pathology Site	**Study Type**	**Morphology**	**Staining**	**Pathologic Diagnosis**
Right Level II-III Nodal Conglomerate	FNA	Malignant cells with high nuclear-cytoplasmic ratio, inconspicuous nucleoli and irregular nuclear borders in small clusters in a background of necrosis	p40: negative CD56: patchy positivity p16: negative	Poorly differentiated carcinoma
Right Posterior Oropharyngeal Wall Mass	Directed Surgical Biopsy	Diffuse nested growth pattern with palisading at the periphery of the nests and central necrosis. These tumor cells were polygonal, with large, hyperchromatic nuclei and moderate cytoplasm, and small nucleoli. There were numerous mitotic figures	CD56: positive p40: negative CK5/6: negative Synaptophysin/Chromogranin: negative p16: negative	Combined SCC and LCNEC
		Large, atypical, pleomorphic non-keratinizing squamous cells with focal intracellular bridging, and occasional prominent nucleoli.	p40: positive CK5/6: positive p16: negative	
Lower Paratracheal Lymph Node	EBUS-guided FNA	Medium-large atypical, pleomorphic cells with large, hyperchromatic nuclei, and small nucleoli	p40: negative CD56: strongly positive Synaptophysin/Chromogranin: rarely positive	High-grade LCNEC

Abbreviations: FNA, fine needle aspiration; EBUS, endobronchial ultrasound.

of advanced H&N cancers; the oropharynx is no exception, as pulmonary metastases account for roughly half of all cases of metastatic oropharyngeal SCC.[23,24] In general, distant metastasis to the oropharynx is atypical, with the most common site of primary malignancies including lungs, kidneys, prostate for men, and breast for women.[25] This is more commonly seen in advanced and recurrent disease.

Outside of the H&N, a small number of case reports in the literature describe combined LCNEC and SCC in the gastrointestinal tract, specifically in the colon and rectum.[26–29] Munakata et al. reported this rare case of colon cancer, although final pathologic examination suggested the primary lesion likely originated from the lung.[26] Conversely, Woischke et al. present two cases of combined LCNEC and SCC of the colon with histologic and genetic evidence of local origin in the colon.[27] Furthermore, the authors present genetic evidence of mutations of the *FBXW7* gene leading to upregulation of the Wnt-signaling pathway, a possible pathophysiologic explanation for local tumorigenesis of this rare combined malignancy. This might provide insight into similar genetic and pathophysiologic mechanisms at play in the H&N. Authors have identified a subset of sinonasal and oropharyngeal LCNEC as being related to HPV infection[30]; however, to date, current guidelines set by the College of American Pathologists endorse HPV testing only on newly-diagnosed oropharyngeal SCC, as these are the only subset of tumors that have been shown to have an improved prognosis with HPV-positivity.[31] Nonetheless, some authors have advocated for HPV testing in select cases, such as when analyzing metastatic LCNEC to establish a primary tumor source.[32]

Due to its rarity, clinical management of LCNEC of the H&N remains an unstandardized topic with little evidence in the literature and no randomized controlled trials to guide management options.[33] Previous authors have made recommendations by looking to the pulmonary literature for treatment option of either LCNEC or small cell NEC of the lung; however, prognosis has varied dramatically between studies, and no consensus has been reached.[1,9,11,34] In most tumors, systemic therapy targeted against possible micrometastases is recommended.[33] Trimodal therapy has been recommended for LCNEC of the H&N, but survival remains poor in most cases.

In the case presented herein, it was unclear whether the combined LCNEC and SCC of the oropharynx arose from local tumorigenesis, metastatic spread, or both. However, the subsequent paratracheal lymph node biopsy revealing LCNEC provided evidence that the primary source of the neuroendocrine component in this case was most likely pulmonary, with a local oropharyngeal SCC arising in the classic fashion. The patient was therefore treated with chemotherapy targeted at both unique histopathological components. More research will be needed to determine the optimal treatment approach for combined NEC tumors of the H&N.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

AUTHOR CONTRIBUTIONS

Rossi, Gietzen, Malaya, Haroun, and Conner involved in drafting and editing of manuscript. Clement, Resto, Joshi, and Coblens involved in concept, guidance, and review of manuscript.

ETHICAL APPROVAL

The patient presented in the case report herein provided written consent.

CONSENT

Written informed consent was obtained from the patient.

DATA AVAILABILITY STATEMENT

Due to the case report format of this manuscript, all data were obtained from the medical chart of the patient plus pre-existing literature. The data obtained from the medical chart are protected for patient privacy.

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