



Small Cell Neuroendocrine of the Head and Neck: A Rare Presentation and Review of the Literature

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Abstract

Head and neck tumors account for roughly 3% of malignancies in the United States and about 90% of these tumors are squamous cell cancers. Neuroendocrine neoplasms arise from neural crest cells and are commonly found in the gastrointestinal tract. Neuroendocrine neoplasms arising from the head and neck tend to be rare. In this article, we present a rare case of human papilloma virus–associated poorly differentiated small cell neuroendocrine carcinoma (NEC). Our patient was a 62-year-old African American man who presented with worsening left-sided neck pain and swelling that started 3 months prior to presentation, associated with an unintentional 20-pound weight loss over 6 months, hoarseness in his voice, in addition to dysphagia and odynophagia. Biopsy of left-sided tongue mass revealed poorly differentiated small cell NEC that was positive for HPV (E6/E7) RNA in situ hybridization. Patient was found to have metastatic disease at the time of diagnosis and given the aggressive nature of small cell NECs and the patient's symptomatic burden, chemotherapy with cisplatin and etoposide was initiated in the hospital. The patient was subsequently discharged from the hospital and is continuing treatment outpatient with cisplatin, etoposide, and atezolizumab.

Keywords

hematology oncology, pathology, head and neck cancer, neuroendocrine carcinoma

Introduction

Tumors of the head and neck usually account for 3% of malignancies in the United States¹ and account for 66000 annual cases and 15000 deaths. The primary causes of head and neck cancers are alcohol and smoking use, as well as human papilloma virus (HPV) infection.² More than 90% of oropharyngeal cancers are squamous cell cancers,³ and neuroendocrine neoplasms (NENs) make up a small proportion of head and neck cancers. Neuroendocrine neoplasms are a rare and heterogeneous group of tumors, making up around 2% of all malignancies, and tend to be more common in women.⁴ Neuroendocrine neoplasms arise from neural crest cells, thus can have various originating sites in the body. Neuroendocrine neoplasms commonly arise in the gastrointestinal tract; however, they can also be found in the lungs and the pancreas.⁴ Regardless of the site of origin, cells from NENs tend to express synaptophysin and chromogranin A.⁵ Neuroendocrine neoplasms of the head and neck tend to be rare; with the most common tumor histology of this anatomical region being squamous cell carcinoma, arising from squamous cells that line the mucosal surface. Recently, the World Health Organization published classification

guidelines for head and neck tumors,⁶ where NENs are divided into 2 categories: well-differentiated neuroendocrine tumors (NETs) and poorly differentiated neuroendocrine carcinomas (NECs). Well-differentiated NETs are divided into 3 grades (G1-G3) based on mitotic activity, proliferative rate, and/or presence of necrosis. Poorly differentiated NECs are high grade (increased mitotic activity/proliferative rate/presence of necrosis) and are subdivided into small cell NEC or large cell NEC based on morphology. Neuroendocrine neoplasms are treated differently based on their aggressiveness as dictated by pathology. Here, we report a case of rapidly progressing poorly

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Figure 1. Computed Tomography (CT) soft tissue of neck. Enhancing mass lesion in the tongue, slightly lateralized to the left side measuring about the $4.4 \times 3.7 \times 4.3$ in transverse, AP and CC directions. The lesion involves both vallecula with probable involvement of ventral surface of epiglottis. There is extensive necrotic lymphadenopathy on left side of the neck involving left level 2 through level 4 regions. Most of these lymph nodes measure about 3 to 4 cm in size.

differentiated small cell NEC of the head and neck in a patient who presented with unilateral neck swelling and trouble swallowing.

Case Presentation

Our patient was a 62-year-old African American man with type 2 diabetes mellitus, hyperlipidemia, and a history of an aortic aneurysm with a mechanical aortic valve replacement who presented to the emergency room for worsening left-sided neck pain and swelling that started 3 months prior to presentation, associated with an unintentional 20-pound weight loss over 6 months, hoarseness in his voice, in addition to dysphagia and odynophagia. He was seen by his primary care physician who noted significant lymphadenopathy of the head and neck on physical examination. He was subsequently referred to medical oncology who obtained dedicated computed tomography (CT) of the soft tissue of the neck which showed an enhancing mass lesion in the tongue measuring about $4.4 \times 3.7 \times 4.3$ cm³ with extensive necrotic lymphadenopathy on the left side of the neck involving level 2 through level 4 with most nodes measuring 3 to 4 cm in size (Figure 1). Computed tomography thorax and CT abdomen pelvis showed evidence of pulmonary, liver, and possible bone metastases. Unfortunately, the patient's clinical

condition rapidly declined, and before the patient was able to get a biopsy, he sought emergency care at our hospital for management of failure to thrive in the setting of worsening dysphagia, odynophagia leading to significant anorexia. An ear, nose, and throat (ENT) evaluation led to a nasopharyngolaryngoscopy which demonstrated a large left base of tongue mass with posterior displacement of the epiglottis. The patient was admitted to the medical intensive care unit for airway observation and further management.

A biopsy of the left neck mass was pursued revealing small cell NEC, likely representing a metastasis from the tongue mass (Figure 2). The left neck mass was also positive for HPV (E6/E7) RNA in situ hybridization, supporting that the small cell NEC was associated with high-risk HPV. Unlike HPV-mediated oropharyngeal squamous cell carcinoma, HPV-mediated small cell NECs are noted to have aggressive clinical behavior. Given that small cell NENs in the head and neck are rare, it was recommended that patient has tongue biopsy performed by ENT to confirm origin of primary site, in addition to a liver biopsy to rule out a second primary malignancy. Biopsy from the base of the tongue revealed mostly necrotic material and crushed cells with features suggestive of a neoplasm with neuroendocrine differentiation (Figure 3), and core biopsies taken from the liver lesion revealed small cell NEC (Figure 4). Overall, the tumor cells were positive for CAM 5.2, pancytokeratin AE1/AE3, CD56, P16, and synaptophysin but were negative for chromogranin, P40, P63, TTF-1, CDX2, CK20, and CD20. Thereby, it was determined the patient had an advanced neuroendocrine malignancy, consistent with head and neck primary.

Given the aggressive nature of small cell NECs and the patient's symptomatic burden, chemotherapy with cisplatin and etoposide was initiated in the hospital. After the first cycle of treatment, the patient had a dramatic improvement in his symptoms, with almost immediate relief of voice hoarseness, left-sided neck pain, and neck swelling. The patient was subsequently discharged from the hospital and is continuing treatment outpatient with cisplatin, etoposide, and atezolizumab. He is currently undergoing cycle 4 of treatment and has had an excellent radiographic and clinical response to chemotherapy and immunotherapy thus far.

Discussion

Head and neck cancers predominantly originate from squamous cells and have an association with alcohol use, smoking, and HPV infection. Neuroendocrine neoplasms of the head and neck are extremely rare neoplasms and may arise from epithelial or neuronal origin.⁷ They are classified based on the site of origin, histopathology proliferation index, mitotic rate count, and absence/presence of necrosis.^{6,8} There is limited data regarding the frequency, prognosis, and site of head and neck NENs.⁹ A SEER database review by Khan et al⁹ found that head and neck NEN

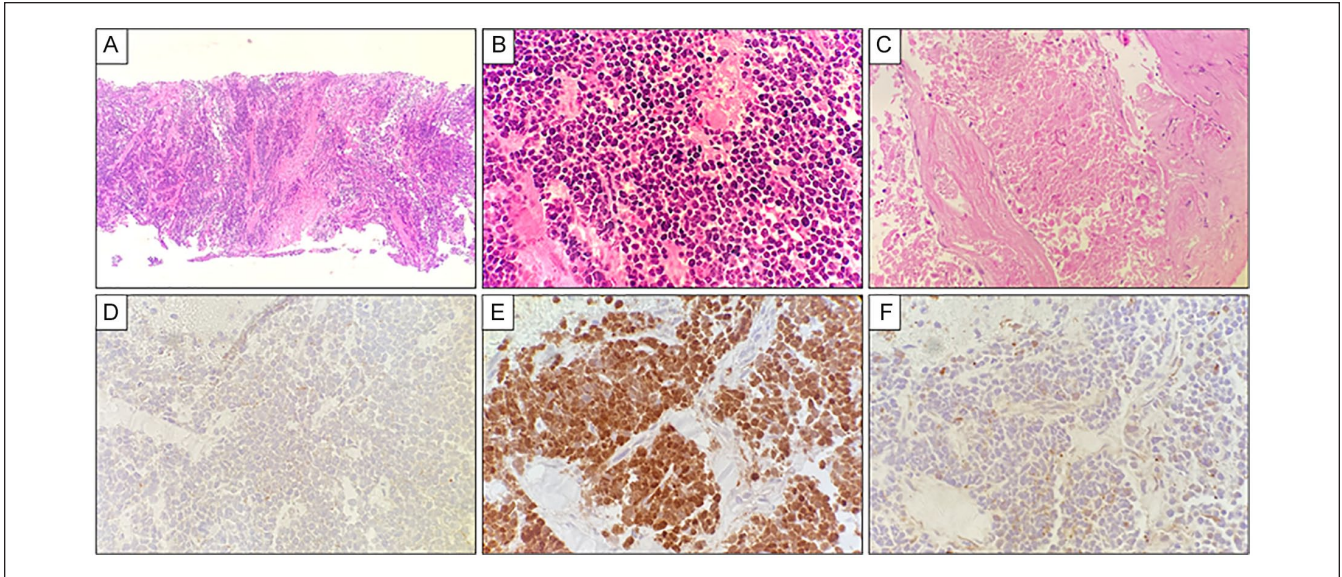


Figure 2. (A) Hematoxylin and eosin, Magnification 10x. Biopsy cores from the left neck mass shows tissue infiltrated by high-grade poorly differentiated carcinoma with a solid nested to trabecular pattern. (B) Hematoxylin and eosin, Magnification 40x. The tumor cells have high nuclear/cytoplasmic (N/C) ratio with increased mitotic activity and occasional molding. (C) Hematoxylin and eosin, Magnification 20x. Intermittent sheet-like segments of tumor cell necrosis are present. (D-F) Synaptophysin, P16, and pancytokeratin AE1/AE3 immunostains, Magnification 40x. The tumor cells are positive for synaptophysin, P16, and pancytokeratin AE1/AE3. The morphology and immunoprofile fit with small cell neuroendocrine carcinoma. The limited positive staining seen in the synaptophysin and pancytokeratin AE1/AE3 immunostains is expected since the tumor cells have limited cytoplasm.

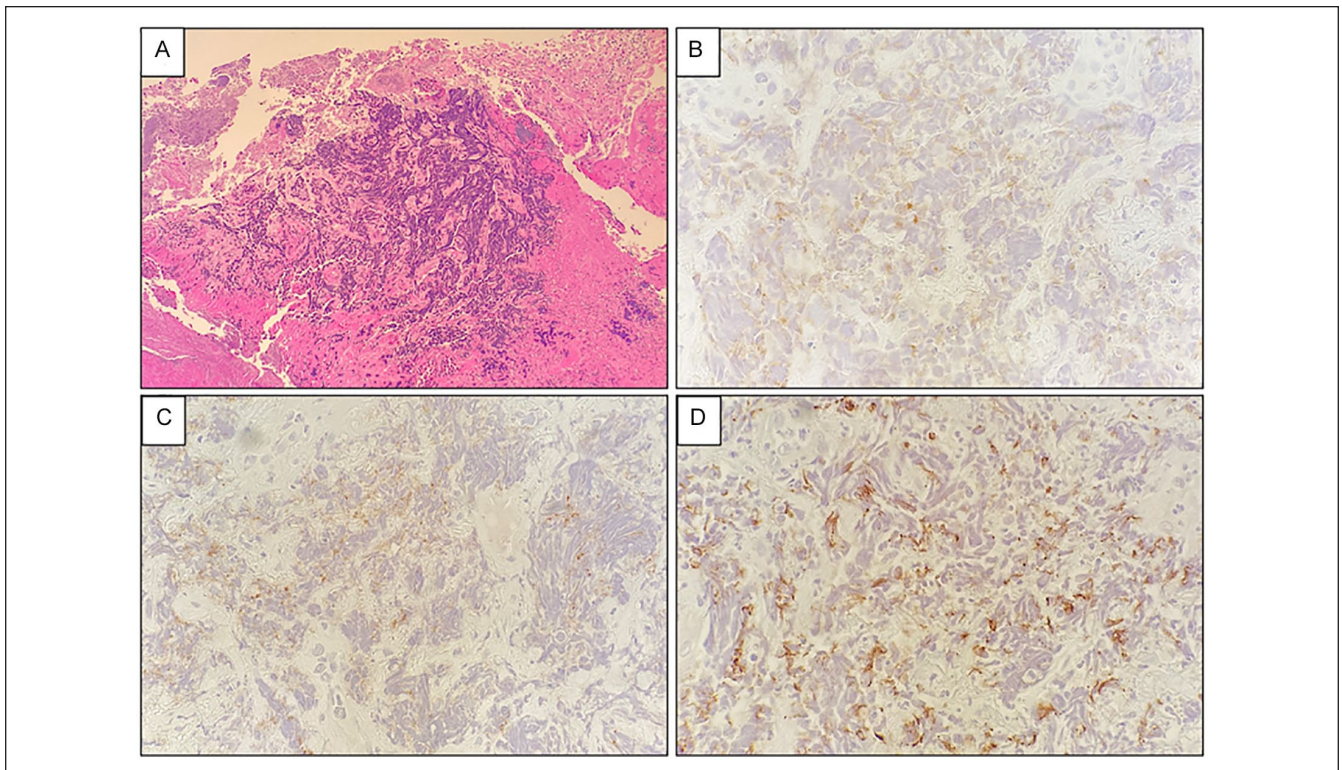


Figure 3. (A) Hematoxylin and eosin, Magnification 10x. Biopsy cores from the left base of tongue display mostly necrotic material and crushed cells. (B-D) Synaptophysin, CD56, and pancytokeratin AE1/AE3 immunohistochemical stains, Magnification 40x. The crushed cells show positivity for synaptophysin, CD56, and pancytokeratin AE1/AE3. The overall features fit with a neoplasm with neuroendocrine differentiation. The limited positive staining seen in the immunostains is expected since the tumor cells have limited cytoplasm.

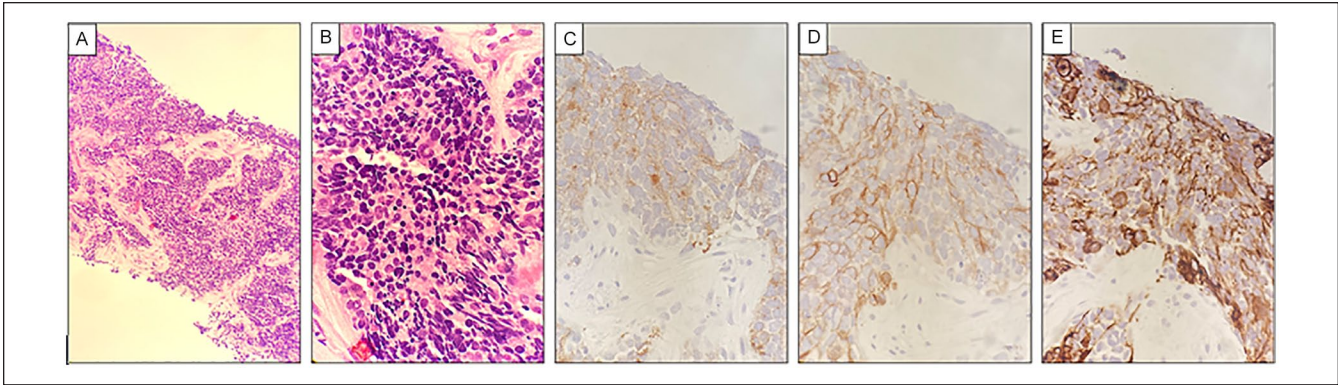


Figure 4. (A) Hematoxylin and eosin, Magnification 10x. Sections from the liver lesion biopsy contain liver parenchyma with extensive infiltration by small cell neuroendocrine carcinoma. (B) Hematoxylin and eosin, Magnification 40x. The tumor cells are small with fine chromatin and inconspicuous nucleoli. The majority of the tumor cells have scant to limited cytoplasm with occasional nuclear molding. Occasional slightly larger cells with mildly increased cytoplasm are seen and appear to be the same tumor cells with “intermediate” morphology. Scattered mitotic figures and single cell necrosis are present. (C-E) Synaptophysin, CD56, and pancytokeratin AE1/AE3 immunohistochemical stains, Magnification 40x. The tumor cells are positive for synaptophysin, CD56, and pancytokeratin AE1/AE3. The limited positive staining seen in the immunostains is expected since the tumor cells have limited cytoplasm.

survival varied significantly based on site and metastatic status, with oropharyngeal tumors having the poorest prognosis. A small case series of 14 patients with NENs of the head and neck by Mitchell et al⁷ found that this subset of patients had better survival rates than NENs of the lung but worse survival rates when compared with squamous cell cancers of the head and neck. Previous studies have found that small cell NENs have a 5-year disease-specific survival rate of 19.3%¹⁰ in spite of treatment. In addition, our patient’s mass was positive for HPV (E6/E7) RNA in situ hybridization. According to the literature, HPV-related high-grade NEN is very rare and has only been reported in few case reports.¹¹ Previous case reports have found that these tumors are associated with progressive disease and are extremely aggressive.¹²

Extrapulmonary small cell carcinomas are very rare, with head and neck disease comprising only 14% of extrapulmonary small cell neoplasms.¹³ These neoplasms are characterized by an aggressive natural history and often have widespread metastatic disease on presentation.¹⁴ There are no randomized control trials to support the treatment guidelines. In our case, our patient was presented with a large left-sided neck mass and was found to have stage IV disease with liver involvement. Due to the significant burden of disease on presentation with left-sided neck swelling, dysphagia, odynophagia, and concern for impending airway compromise, the decision was made to initiate palliative chemotherapy in the hospital. As per National Comprehensive Cancer Network (NCCN) recommendations, it is recommended to treat these patients with platinum-based regimens in combination with etoposide. However, it should be noted that these guidelines are based on 2 very small retrospective studies including 21 and 19 patients, respectively, for cisplatin¹⁵ and carboplatin¹⁶ regimens in combination with etoposide. Data

are predominately extrapolated from treatment for NEC of the hepatobiliary tract and pancreas. Based on these retrospective analyses and NCCN guidelines, our patient was initiated on an inpatient chemotherapy regimen with cisplatin 80 mg/m² and etoposide 100 mg/m² that he tolerated well with significant reduction of tumor size and symptomatic improvement. The patient has since been discharged from the inpatient unit and is following up outpatient for continued chemotherapy and immunotherapy, with atezolizumab added to the regimen.

Conclusion

Neuroendocrine neoplasms of the head and neck are a rare entity, which when diagnosed, must be treated promptly to prevent potential life-threatening compromise given the primary site and concern for airway compromise. Our patient had HPV-associated small cell NEC, which has only been reported in a handful of cases. Given the rarity of these tumors, we want to highlight the aggressive nature of those that do arise. We reviewed the limited data available to prognosticate this disease and the management of NENs of the head and neck.

Declaration of Conflicting Interests

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Ethics Approval

Our institution does not require ethical approval for reporting individual cases or case series.

Informed Consent

Written informed consent was obtained from the patient for their anonymized information to be published in this article.

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