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p16 positive oropharyngeal small cell cancer: A case report

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ABSTRACT

Extra-pulmonary small cell carcinomas (EPSCC) are rare malignancies. Like small cell lung cancer (SCLC), they are aggressive malignancies with dismal prognosis. We here report a case of a middle-aged man who presented with odynophagia and cervical lymphadenopathy. Diagnostic workup confirmed the diagnosis of locally-advanced p16-positive oropharyngeal cancer (OPC) with a surprising histology of small cell cancer, suggesting a human papilloma virus (HPV)-related oropharyngeal cancer with small cell differentiation. HPV oropharynx infection is a well-known risk factor for squamous cell carcinoma of the oropharynx, but it is unknown if it may increase the risk of other OPC histology.

Introduction

Small cell carcinoma (SmCC) is an aggressive malignancy that occurs mainly in the lungs secondary to cigarette smoking. It is defined by World Health Organization as poorly differentiated neuroendocrine tumors, and marked by the presence of neurosecretory granules in its tumor cells. Though rare, extra-pulmonary small cell carcinomas (EPSCCs) have also been reported at a rate of 5.8% of SmCC cases [1]. The most frequent EPSCCs involve the gastrointestinal and genitourinary systems, including the esophagus, stomach, colon, rectum, anus, gallbladder, cervix, vagina, prostate, and bladder. EPSCC has been described in nearly every organ system [2], with head and neck constituting 11–21% of all EPSCC [1]. Oropharyngeal presentation of SmCCs has been reported with an incidence rate of 0.003 per 100,000 [3]. Risk factors like tobacco and alcohol have been linked as possible etiologies for EPSCC [4]. Also, contrary to p16+ oropharyngeal squamous cell carcinoma, which are proven to be related to human papillomavirus (HPV) oropharyngeal infection and to have better prognosis in comparison to other squamous cell cancers of the same region [5], p16+ oropharyngeal (OP) SmCCs may or may not have a cause-effect relationship to HPV, and the aggressive clinical behavior of SmCC may overwhelm the prognosis benefit of HPV related tumors. The role of HPV on the pathogenesis of SmCC is not clear [6]. Due to the rare incidence of this cancer, more data is needed to better understand the presentation, pathology, immunohistochemistry and treatment modalities; and thus, we present a rare case of SmCC on the epiglottis.

Case presentation

A 52-year-old man with minimal smoking history presented with odynophagia and a palpable neck mass. Physical examination revealed a polyploid mass in the right oropharynx and enlarged lymph nodes at the right anterior cervical region. A contrast-enhanced CT of the neck showed a right-sided level 2/3 cervical lymphadenopathy composed of conglomerated masses with the largest being 2.7 cm with ill-defined margins concerning for extracapsular spread (N3b), and a 2.9 cm mass at the right base of the tongue infiltrating the proximal lingual surface of the epiglottis (T3) (Fig. 1A). Further imaging showed no other lesions in the brain, head and neck, chest, or abdomen (cT3N1M0, clinical Stage III). Similarly, PET scan and MRI of the brain did not reveal any distant metastases.

The fine needle aspiration of the neck mass was positive for malignant cells. A follow up core biopsy demonstrated nests and sheets of round to oval small neoplastic cells (Fig. 2A). The neoplastic cells had indistinct cell borders, scant cytoplasm, hyperchromatic nuclei, fine granular (salt and pepper) chromatin with no distinct nucleoli. Nuclear modeling and smudging with scattered brisk mitotic activity were also evident (Fig. 2B). The neoplastic cells were immunoreactive to TTF-1 (Fig. 2C), Synaptophysin (Fig. 2D) and p16 (Fig. 2E). They were non-immunoreactive to chromogranin, p40, p63 and Napsin. The morphology and immune-profile was consistent with the diagnosis of metastatic p16 positive SmCC.

The patient was diagnosed with locally-advanced SmCC of the oropharynx (T3N3b; stage IVB AJCC 8th edition) and treated with concurrent chemoradiation utilizing cisplatin and etoposide and definitive radiation dose of 6600 cGy/33 fractions, followed by 2 cycles of chemotherapy to complete a course of 4 cycles of systemic therapy. Repeat imaging after chemoradiation and 4 cycles of chemotherapy showed complete response with no evidence of disease (Fig. 1B). The patient continues to be in remission for 14 months.

Discussion

This is a very rare case of SmCC of the oropharynx. As in our case, the classic and distinctive histologic findings on hematoxylin and eosin are sufficient to make the diagnosis. In support of the diagnosis, synaptophysin and chromogranin were positive. Due to the lack of specific treatment protocols for this condition, the most reasonable approach was to adapt a plan similar to that of lung SmCC [7]. Since chemoradiation has been reported to yield the best 5-year disease-specific survival as compared to other modalities (31% versus 13%) [1], chemoradiation was warranted in treating this patient. This patient

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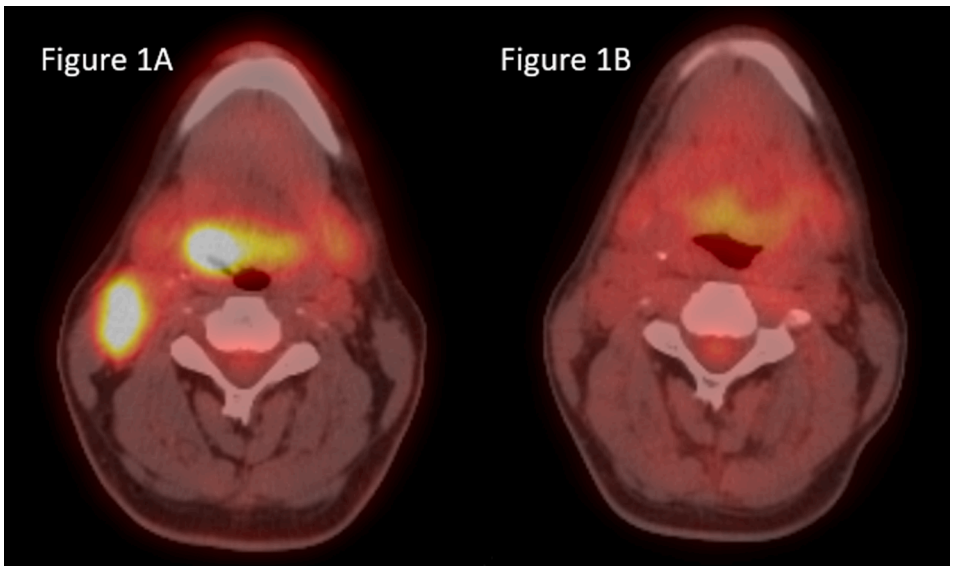

Fig. 1. (A) shows the pre-treatment PET scan and (B) demonstrates the complete response seen post-treatment.

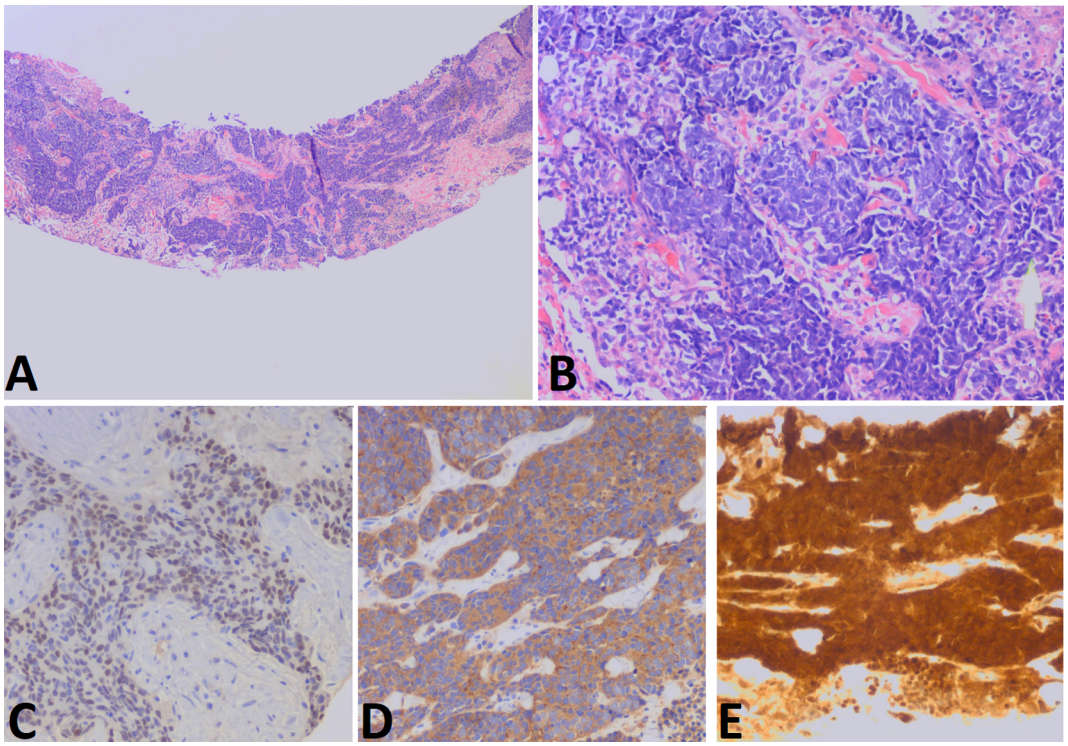

Fig. 2. The Hematoxylin and Eosin (H&E) histology sections of the core biopsy demonstrate nests and sheets of round to oval small neoplastic cells (A). The neoplastic cells have indistinct cell borders, scant cytoplasm, hyperchromatic nuclei, fine granular (salt and paper) chromatin with no distinct nucleoli. Nuclear molding and smudging with scattered brisk mitotic activity are also evident (B). The neoplastic cells are immunoreactive to TTF-1 (C), Synaptophysin (D) and P16 (E). They are non-immunoreactive to chromogranin, P40, P63 and Napsin. The morphology and the immunoprofile is consistent with the diagnosis of metastatic P16 positive small cell carcinoma.

received treatment mirroring the current paradigm for limited stage small cell lung cancer leading to a complete response after 4 cycles. One case series used neoadjuvant chemotherapy for varying number of cycles followed by chemoradiation [1].

The association between HPV and oropharyngeal squamous cell carcinoma (p16-positive OPCs) is well established and so is the HPV status as an independent prognostic factor [8,9]. On the other hand, p16 positivity in SmCC of the oropharynx might not carry a similar favorable prognostic value. In fact, p16 positivity might not be reflective of HPV infection. Alos et al described a series of 14 SmCC cases of the head and neck; all of which were strongly positive for p-16 but negative for HPV by in situ hybridization and PCR. Eleven of them had loss of protein retinoblastoma 1 (Rb1) [10]. However, Kraft et al reported 8 cases of oropharyngeal SmCC; of which 7 overexpressed p16 and 6 had a confirmed HPV infection by in situ hybridization and/or PCR [11]. While loss of Rb1 is almost ubiquitous in SCLC [12–13], the role of this in the tumorigenesis of EPSCC is not clear.

Conclusion

We report a rare case of extrapulmonary small cell carcinoma originating from the oropharynx. A multidisciplinary approach was essential for diagnosing and treating this patient. He achieved a complete response with definitive chemoradiation and a total of 4 cycles of systemic chemotherapy. The role of p16 positivity and correlation with HPV infection remains to be further studied.

Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: 'The authors have not received any funding for this study and declare no direct conflict of interest. Unrelated to this manuscript, Dr. Nagasaka has been awarded the 2020 Karmanos Cancer Institute Cancer Immunology and Immunotherapy Pilot Award (P30 CA022453). Dr. Nagasaka serves on the advisory board for AstraZeneca, Caris Life Sciences, Daiichi-Sankyo, Takeda, Novartis, EMD Serono, Blueprint, JNJ, Pfizer and Lilly and has received study funding from Tempus. Dr. Sukari serves on the advisory board for Merck and Eisai. He has received study funding from Eisai. All other authors have no potential conflict of interest to declare'.

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