Journal of Oral and Maxillofacial Surgery, Medicine, and Pathology xxx (2016) xxx–xxx

Contents lists available at ScienceDirect

Journal of Oral and Maxillofacial Surgery, Medicine, and Pathology

journal homepage: www.elsevier.com/locate/jomsmp

Case Report

Human papillomavirus-related mixed non-keratinizing squamous cell carcinoma of the palatine tonsil with small cell neuroendocrine carcinoma: Report of a case

Yue Ma [a], Ninad Patil [b], Jean-Pierre Gagner [b,1], Brett A. Miles [a,*]

[a] Department of Otolaryngology Head and Neck Surgery, Icahn School of Medicine at Mount Sinai, New York, NY 10029, USA
[b] Department of Pathology, Icahn School of Medicine at Mount Sinai, New York, NY 10029, USA

ARTICLE INFO

Article history:
Received 30 October 2014
Received in revised form
15 September 2016
Accepted 23 September 2016
Available online xxx

Keywords:
Neuroendocrine carcinoma
Squamous cell carcinoma
Human papillomavirus
Tonsillar carcinoma
Small lymphocytic lymphoma/chronic lymphocytic leukemia

ABSTRACT

Increased testing for human papillomavirus (HPV) in oropharyngeal carcinomas has broadened the range of HPV-associated malignancies identified at this site. While HPV-related oropharyngeal non-keratinizing squamous cell carcinomas (SCC) are known to have a better prognosis than their non-HPV counterparts, HPV positivity may not alter the aggressive nature of HPV-associated small cell neuroendocrine carcinomas (SCNEC). We report a unique case of a mixed non-keratinizing type HPV-associated tonsillar SCC with SCNEC differentiation, and provide a comparison with the rare reported cases of such mixed carcinomas in the literature. Our patient is only the second such case positive for HPV genotype 18 and the only case in which this HPV-related mixed tonsillar tumor occurred in a patient with small lymphocytic lymphoma/chronic lymphocytic leukemia (SLL/CLL). The case discussion supports the concept that HPV positivity does not confer a better prognosis in such mixed non-keratinizing type SCC with SCNEC. Our report also alerts pathologists to the need to evaluate for the possibility of a coexisting neuroendocrine component when oropharyngeal squamous cell carcinoma (OPSCC) is diagnosed, as its presence will affect the patients' clinical management and prognosis.

1. Introduction

The vast majority of human papillomavirus (HPV)-related oropharyngeal carcinomas are of squamous cell non-keratinizing type. As HPV testing is now routinely performed in oropharyngeal carcinomas, we have become aware of the non-squamous diversity of HPV-associated malignancies at this location [1,2]. Studies have demonstrated a strong association of neuroendocrine carcinomas with oncogenic HPV infection in the oropharynx [3–5]. One subtype of neuroendocrine carcinomas, small cell neuroendocrine carcinomas (SCNEC) represent a rare, novel HPV-associated entity [3–5]. SCNEC represent a group of aggressive malignancies with high tumor grade and poor clinical outcome. Although HPV-related oropharyngeal squamous cell carcinomas (OPSCC) generally have a favorable clinical prognosis, it is unknown, however, whether HPV positivity confers a better prognosis in patients with a mixed non-keratinizing SCC and SCNEC pathology. To the best of our knowledge, only six cases of mixed HPV-positive non-keratinizing SCC with SCNEC have been reported [4,5]. Here, we report a case of a 64 year-old non-smoking male with this rare entity.

2. Report of a case

The patient was a 64 year-old Caucasian male who presented with neck pain and dysphagia for two months. Social history was significant for having more than 6 sexual partners over his lifetime; however, the patient had no history of tobacco or excessive alcohol use. Physical examination revealed fullness in the right palatine tonsil and a 3-cm right neck mass. Computerized tomography (CT) of the head and neck with contrast demonstrated a mass lesion arising from the region of the right oropharynx consistent with a tonsillar mass (Fig. 1A) and evidence of cervical nodal metastasis. Biopsy of the right tonsil revealed a poorly-differentiated SCC positive for p16. Interestingly however, fine

* Corresponding author at: One Gustave L. Levy Place, Box 1189, New York, NY 10029-3136, USA. Fax: +1 212 427 4088.
E-mail addresses: yue.ma@mountsinai.org (Y. Ma), ninad.patil@mountsinai.org (N. Patil), jpmg01@gmail.com (J.-P. Gagner), brett.miles@mountsinai.org (B.A. Miles).
[1] Present address: Department of Pathology, New York University School of Medicine, New York, NY 10016, USA.

http://dx.doi.org/10.1016/j.ajoms.2016.09.010
2212-5558/

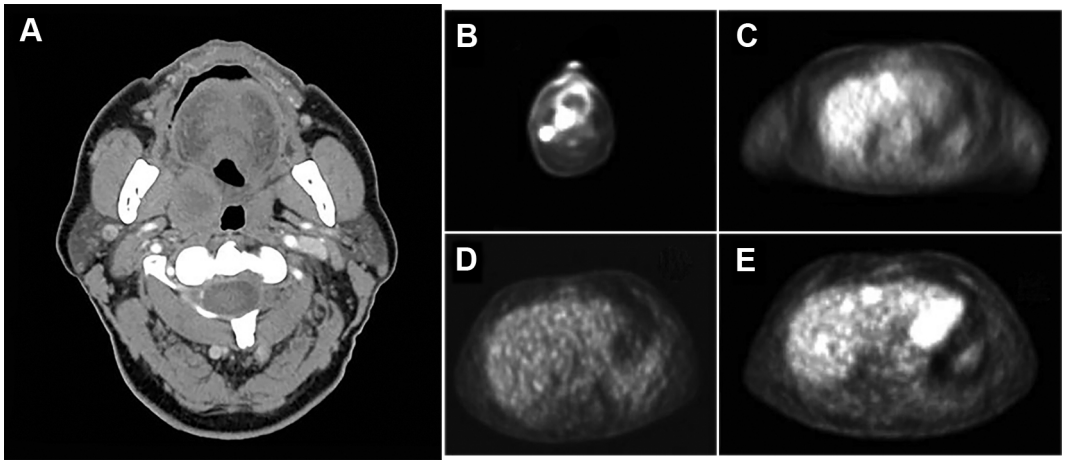

Fig. 1. (A) Axial CT scan showed a mass arising from the right palatine tonsil. (B and C) Axial FDG–PET showed a right tonsillar mass and liver metastasis at diagnosis. (D) Initial response to chemotherapy evaluated by axial FDG–PET showed complete resolution of the hepatic lesions. (E) Follow-up axial FDG–PET showed rapid return of disease with interval development of multiple hepatic lesions at 10 weeks after chemotherapy.

needle aspiration biopsy of the neck mass was consistent with a high-grade malignancy with neuroendocrine features, compatible with small cell carcinoma. Fluorodeoxyglucose positron emission tomography (FDG–PET) demonstrated increased FDG uptake in the right tonsil, neck and liver (Fig. 1B and C). Fine needle aspiration and core needle biopsy of the liver was consistent with a high-grade neuroendocrine tumor (Fig. 2A and B).

The patient received treatment for presumed primary SCC of the right tonsil and metastatic small cell carcinoma with unknown primary. The patient was treated with 6 cycles of cisplatin and etoposide and demonstrated an excellent response with complete resolution of the hepatic lesions as shown by FDG-PET (Fig. 1D). Follow-up FDG–PET at 10 weeks after chemotherapy, however, showed significant interval progression of metastatic disease within the right tonsillar fossa, right neck, right retropharyngeal region and liver (Fig. 1E). The patient had several episodes of tonsillar bleeding and, after discussion of this case at multidisciplinary tumor board, the patient underwent transoral robotic radical tonsillectomy, partial pharyngectomy and a right selective neck dissection (levels II–IV).

Following surgical resection, the right tonsillar specimen was found to show *in situ* and invasive SCC, non-keratinizing type with maturation. Numerous scattered foci of SCNEC were seen arising from the *in situ* and invasive components of the squamous carcinoma (Fig. 2C). The neuroendocrine cells demonstrated abundant apoptoses and mitoses (Fig. 2D). Patches of atypical lymphoid infiltrates were also present in the surrounding tissue. Fifteen levels II–IV neck lymph nodes were involved by metastatic carcinoma, which also showed a mixture of carcinoma with squamous and neuroendocrine morphology. Immunohistochemical studies on the primary tonsillar tumor as well as the lymph node metastases showed that the neuroendocrine component was chromogranin (Fig. 2E) and synaptophysin positive and the squamous component was cytokeratin 5/6 (CK 5/6) positive (Fig. 2F). p16 was diffusely immunoreactive in both the SCC and SCNEC components (Fig. 2G and H). Thyroid transcription factor-1 (TTF-1) was immunoreactive only in the neuroendocrine areas.

Polymerase chain reaction (PCR) analysis for HPV DNA demonstrated the presence of HPV genotype 18 DNA in both the right tonsillar tumor and the liver biopsy specimens. This result was subsequently confirmed by the finding of HPV 18 type-specific DNA by *in situ* hybridization (ISH) in the tumor tissues. ISH assays for both HPV DNA and mRNA were performed on specimens of the right tonsillar tumor and level II lymph node metastases. Ventana Inform HPV III Family 16 probe set, Dako Wide Spectrum HPV probe set and Dako HPV 18 type-specific probe all detected positive HPV DNA hybridization signals in both squamous and neuroendocrine components of the tonsillar tumor (not shown) but failed to detect HPV DNA in the lymph node metastases. However, transcriptionally active HPV mRNA was detected using RNAscope ISH in the tonsillar tumor (all tumor components identified by their pattern of synaptophysin staining in an adjacent tissue section) (Fig. 2I and J) and the lymph node metastases.

Additionally, the level II lymph nodes demonstrated effaced architecture and pseudofollicular proliferation centers (CD5, CD20 and CD23 immunoreactive but cyclin D1 immunonegative), consistent with small lymphocytic lymphoma/chronic lymphocytic leukemia (SLL/CLL) (Fig. 2K–M). The previously described patches of atypical lymphoid infiltrates in the tonsil were also consistent with SLL/CLL. Additional work-up for SLL/CLL was not undertaken in light of the advanced stage of the patient's tonsillar tumor.

The possibility of the SCNEC component originating from the lung was ruled out based on evidence of transcriptionally-active-HPV in the SCNEC component (Fig. 2J), and morphologically by the intricate multifocal mixture of both components in the tonsil (Fig. 2C–I) as well as the regional lymph nodes. A final diagnosis of HPV-associated mixed non-keratinizing SCC and SCNEC of the right tonsil, pathologic stage pT2N2bM1, was made.

The patient recovered uneventfully from surgery. Follow-up FDG–PET performed at 10 weeks post-operatively demonstrated extensive disease progression in the neck, pelvic bone, liver, and lungs; he was then started on palliative systemic chemotherapy. The patient subsequently died, 11 months after his initial diagnosis.

3. Methods

3.1. Immunohistochemistry

Immunohistochemical studies were performed on selected formalin-fixed paraffin-embedded (FFPE) tumor sections alongside positive and negative control tissues on the Ventana automated analyzer (Ventana Medical Systems Inc., Tucson, AZ). Primary antibodies used to evaluate the carcinoma were anti-chromogranin A, cytokeratin 5/6 and p16 mouse monoclonal antibodies as well as anti-synaptophysin and thyroid transcription factor-1 rabbit monoclonal antibodies. Additional antibodies used to evaluate the SLL/CLL were anti-CD3, CD5, CD10, CD20, CD23, CD30, CD43, CD79a,

Please cite this article in press as: Ma Y, et al. Human papillomavirus-related mixed non-keratinizing squamous cell carcinoma of the palatine tonsil with small cell neuroendocrine carcinoma: Report of a case. J Oral Maxillofac Surg Med Pathol (2016), http://dx.doi.org/10.1016/j.ajoms.2016.09.010