Accepted Manuscript online: 2024-12-05 Article published online: 2025-01-07

HPV-associated Sinonasal Squamous Cell Carcinoma

Rex H. Lee[1] Annemieke van Zante[2] Ezequiel Goldschmidt[3] Ivan H. El-Sayed[1]

[1] Department of Otolaryngology - Head and Neck Surgery, University of California San Francisco, San Francisco, California, United States
[2] Department of Pathology, University of California San Francisco, San Francisco, California, United States
[3] Department of Neurological Surgery, University of California San Francisco, San Francisco, California, United States

Address for correspondence Ivan H. El-Sayed, MD, Department of Otolaryngology - Head and Neck Surgery, University of California San Francisco, 2233 Post Street, #349, San Francisco, CA 94115, United States (e-mail: ivan.el-sayed@ucsf.edu).

J Neurol Surg Rep 2025;86:e1–e3.

Abstract

Human papillomavirus (HPV)-associated sinonasal squamous cell carcinoma (SNSCC) (HPV+ SNSCC) is a recently recognized entity that accounts for up to one-third of SNSCC. Although at present these cancers are not routinely tested for HPV, the incidence is increasing and HPV+ SNSCC is associated with superior survival outcomes compared with HPV− SNSCC. Here, we present the case of a patient with HPV+ SNSCC treated with endoscopic resection followed by postoperative radiation and review the literature summarizing epidemiology and management of this disease, with emphasis on the importance of HPV testing in SNSCC.

Keywords
- human papillomavirus
- squamous cell carcinoma
- sinonasal
- endoscopic

Introduction

Case Report

A 66-year-old otherwise healthy woman presented with a one-year history of right nasal obstruction, maxillary tenderness, and clear rhinorrhea. Nasal endoscopy revealed a papillary mass along the superior edge of the right inferior turbinate, indiscernible from the middle turbinate and extending into the ethmoid sinuses (►**Fig. 1**). In-office biopsy demonstrated squamous cell carcinoma (SCC) positive for high-risk human papillomavirus (hrHPV) RNA by in situ hybridization. A diagnosis of HPV-related multiphenotypic sinonasal carcinoma was considered but immunohistochemical staining for Sox-10 was negative which, along with histologic findings, supported a diagnosis of HPV-associated sinonasal SCC (HPV+ SNSCC, ►**Fig. 2**). MRI and CT demonstrated a 3-cm mass of the right anterior ethmoids involving the middle turbinate, abutting the right orbit inferomedially without clear orbital invasion (►**Fig. 3**). The patient opted for upfront endoscopic resection, where the tumor was found not to invade the lamina papyracea and all final margins (including olfactory cleft and dura) were negative for carcinoma. She underwent 60 Gy of adjuvant intensity-modulated radiation therapy to the nasal cavity and bilateral neck, and as of most recent follow-up 5 months postoperatively she had normal visual acuity and no evidence of disease.

Literature Review

SNSCC is the most common malignancy of the nasal cavity and paranasal sinuses, accounting for over half of all cases.[1] Although historically, industrial occupational exposures (particularly wood dust) and smoking have been cited as risk factors for this disease, HPV is now recognized as a key etiologic factor in a subset of SNSCC. Population-based data suggests that hrHPV (most commonly HPV16) is detected in up to one-third of all SNSCC.[2–4] As with HPV-associated oropharyngeal SCC (HPV+ OPSCC), the incidence of HPV-associated SNSCC

received
October 21, 2024
accepted after revision
November 24, 2024
accepted manuscript online
December 5, 2024

DOI https://doi.org/10.1055/a-2496-5240.
ISSN 2193-6358.

Georg Thieme Verlag KG, Oswald-Hesse-Straße 50, 70469 Stuttgart, Germany

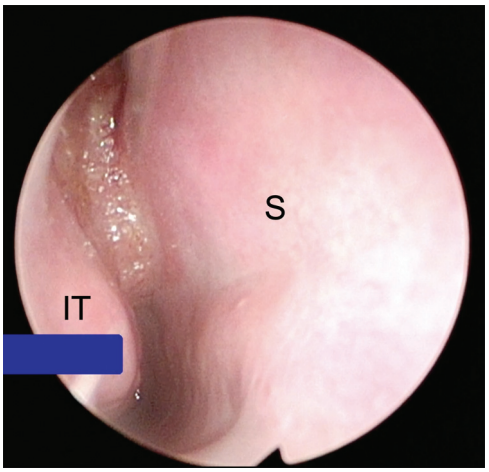

Fig. 1 In-office nasal endoscopy (right nasal cavity depicted) during initial evaluation was notable for a papillary tumor along the superior edge of the right inferior turbinate and indiscernible from the middle turbinate, extending into the right ethmoids and adherent to the septum. IT, inferior turbinate; S, septum.

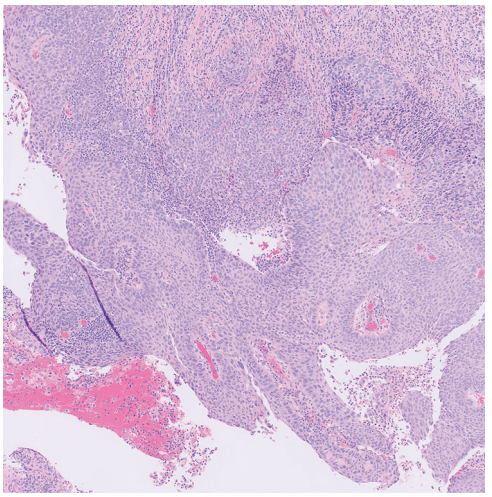

Fig. 2 Hematoxylin and eosin (H&E) tissue section from biopsy performed in the outpatient setting, demonstrating squamous cell carcinoma. The tumor is non-keratinizing with papillary architecture.

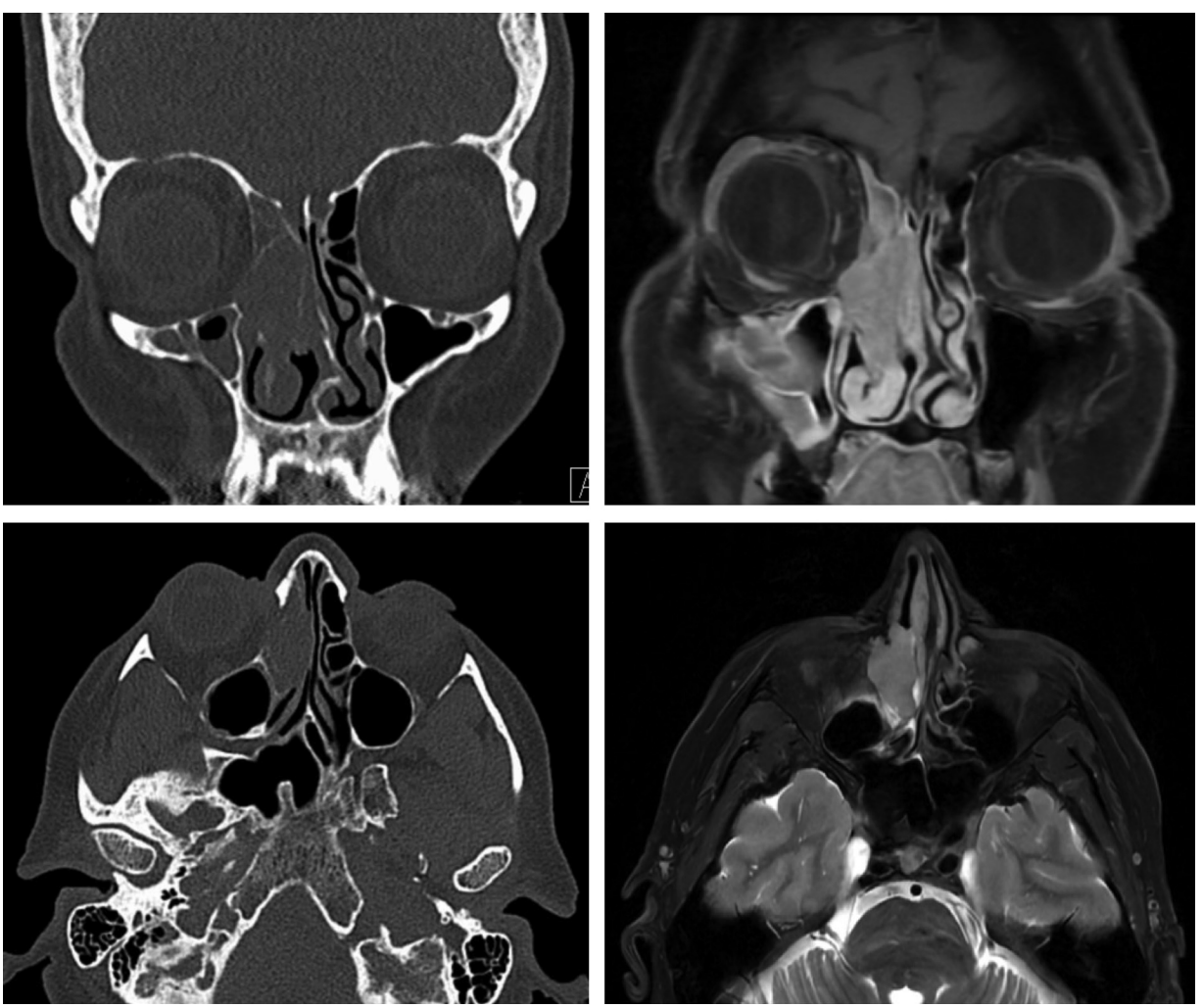

Fig. 3 Preoperative CT images (upper left and lower left) and preoperative T2-weighted MRI images (upper right and lower right) showing a 3-cm mass of the right nasal cavity indiscernible from the right middle turbinate, involving the right anterior ethmoids, and extending into the right maxillary infundibulum. The mass is abutting the right inferomedial orbit but is not exhibiting clear orbital invasion.

(HPV+ SNSCC) has increased significantly over time, especially in younger patients.[4–7]

In oropharyngeal tumors, p16 immunohistochemistry is often used as a surrogate for hrHPV infection.[8] However, p16 positivity is less specific for HPV in the nasal cavity since other sinonasal tumors, such as adenoid cystic carcinoma, are commonly p16+ in the absence of HPV infection.[9] Collective evidence suggests that p16 status is an unacceptable proxy for HPV in non-oropharyngeal tumors.[10] Instead, the gold standard HPV detection method for sinonasal tumors (and all head and neck cancers) is identification of messenger RNA for the HPV viral oncogenes E6/E7 in tumor tissue, most commonly via *in situ* hybridization.[8]

Rates of HPV positivity are highest in SNSCC of the nasal cavity and ethmoid sinuses and lower in the maxillary, frontal, and sphenoid sinuses, ostensibly due to differences in exposure to refluxed oropharyngeal secretions.[3] Recent work suggests the rise of HPV+ SNSCC in recent decades can largely be attributed to an increased incidence of nasal cavity tumors.[11] Currently, there are no differences in management guidelines for HPV+ versus HPV− SNSCC.[1] Upfront surgical resection with curative intent is frequently pursued for resectable SNSCC regardless of HPV status, with adjuvant radiation or chemoradiation recommended for high-risk pathologic features.[1,12,13] Induction chemotherapy is frequently employed in the modern era for locally advanced (T3/T4a) tumors in an attempt to reduce tumor size and allow organ-preserving surgery or radiation, particularly to maximize chances of orbital preservation.[14]

HPV status appears to carry significant prognostic implications in SNSCC. In a large 2019 NCDB study of SNSCC, patients with HPV+ tumors had significantly higher 3-year overall survival compared with those with HPV− tumors (74.6% versus 56.1%, respectively).[4] A 2021 meta-analysis also found substantial differences between HPV+ versus HPV− SNSCC with respect to both 2-year disease-free survival (81.7% versus 55.8%, respectively) and 5-year overall survival (67.6% versus 47.6%, respectively).[15] The apparent survival benefit and high incidence of HPV positivity argues that SNSCC should be routinely tested for HPV. Future study is needed to clarify whether treatment de-escalation, which has been successfully adopted in HPV+ OPSCC, is also appropriate for HPV+ SNSCC.

Conflict of Interest
None declared.

References

1 Thawani R, Kim MS, Arastu A, et al. The contemporary management of cancers of the sinonasal tract in adults. CA Cancer J Clin 2023;73(01):72–112
2 Fukuda K, Shibata A. Exposure-response relationships between woodworking, smoking or passive smoking, and squamous cell neoplasms of the maxillary sinus. Cancer Causes Control 1990;1 (02):165–168
3 Chang Sing Pang KJW, Mur T, Collins L, Rao SR, Faden DL. Human papillomavirus in sinonasal squamous cell carcinoma: a systematic review and meta-analysis. Cancers (Basel) 2020;13(01):45
4 Oliver JR, Lieberman SM, Tam MM, et al. Human papillomavirus and survival of patients with sinonasal squamous cell carcinoma. Cancer 2020;126(07):1413–1423
5 Ramkumar SP, Simpson MC, Adjei Boakye E, et al. High-risk human papillomavirus 16/18 associated with improved survival in sinonasal squamous cell carcinoma. Cancer 2023;129(09): 1372–1383
6 Chowdhury N, Alvi S, Kimura K, et al. Outcomes of HPV-related nasal squamous cell carcinoma. Laryngoscope 2017;127(07): 1600–1603
7 London NR Jr, Windon MJ, Amanian A, et al. Evaluation of the incidence of human papillomavirus-associated squamous cell carcinoma of the sinonasal tract among US adults. JAMA Netw Open 2023;6(02):e2255971
8 Fakhry C, Lacchetti C, Rooper LM, et al. Human papillomavirus testing in head and neck carcinomas: ASCO clinical practice guideline endorsement of the College of American Pathologists guideline. J Clin Oncol 2018;36(31):3152–3161
9 Boland JM, McPhail ED, García JJ, Lewis JE, Schembri-Wismayer DJ. Detection of human papilloma virus and p16 expression in high-grade adenoid cystic carcinoma of the head and neck. Mod Pathol 2012;25(04):529–536
10 Chung CH, Zhang Q, Kong CS, et al. p16 protein expression and human papillomavirus status as prognostic biomarkers of nonoropharyngeal head and neck squamous cell carcinoma. J Clin Oncol 2014;32(35):3930–3938
11 Amanian A, Ishii M, Fakhry C, London NR Jr. Epidemiologic trends in human papillomavirus-associated sinonasal squamous cell carcinoma. JAMA Otolaryngol Head Neck Surg 2024;150(07): 609–618
12 Ferrari M, Taboni S, Carobbio ALC, et al. Sinonasal squamous cell carcinoma, a narrative reappraisal of the current evidence. Cancers (Basel) 2021;13(11):2835
13 NCCN Clinical Practice Guidelines in Oncology. NCCN Guidelines for Head and Neck Cancers. 2024
14 Melder KL, Geltzeiler M. Induction chemotherapy for locoregionally advanced sinonasal squamous cell carcinoma and sinonasal undifferentiated carcinoma: a comprehensive review. Cancers (Basel) 2023;15(15):3798
15 Sharma A, Tang AL, Takiar V, Wise-Draper TM, Langevin SM. Human papillomavirus and survival of sinonasal squamous cell carcinoma patients: a systematic review and meta-analysis. Cancers (Basel) 2021;13(15):3677