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WILEY
Human papillomavirus-related carcinoma with adenoid cystic-like features is a newly described histologic variant of sinonasal tract carcinoma. The implications of this sinonasal malignancy is still being evaluated. There are a limited number of cases reported in the literature, and thus we seek to further characterize this patient population and review the histologic features of this malignancy with the following two cases. The behavior of this entity is as yet uncertain.

**Key Words:** HPV-related carcinoma with adenoid cystic-like features, adenoid cystic carcinoma, sinonasal malignancy.

## INTRODUCTION
Sinonasal malignancies comprise less than 1% of all cancers and roughly 5% of all head and neck cancer. Nevertheless, the low prevalence of sinonasal malignancy is supplemented by a great diversity of neoplasms that may arise in this anatomically complex region. Further, the rarity and peculiar features of some of these neoplasms lends itself to a greater risk of misdiagnosis. For these reasons, sinonasal malignancies remain a challenging area for pathologists and head and neck surgeons alike. Human papillomavirus (HPV)-related carcinoma with adenoid cystic carcinoma (ACC)-like features is a relatively recently described type of sinonasal carcinoma related to HPV. Although this subtype shares morphologic overlap with adenoid-cystic carcinoma, surface level squamous dysplasia is exhibited only by the HPV-related variant. Similarly, it can be distinguished from basaloid squamous carcinoma by the absence of squamous differentiation in the invasive tumor as well as a significant ductal component on histologic analysis.

## CASE REPORT
### Case 1
A 60-year-old man presented due to recurrent epistaxis, pain, and swelling of his palate. The patient was seen in the emergency room, prescribed nasal spray, and referred to oncology. Subsequent biopsy was reported as poorly differentiated squamous cell carcinoma of the nasal cavity. Magnetic resonance imaging revealed a destructive nasal tumor centered on the nasal septum, extending through the hard palate into the roof of the mouth and involving the ethmoids. Imaging revealed that the skull base and orbits were free of disease. The patient underwent transnasal and transpalatal piecemeal resection of the 3.5-cm tumor. Final pathology showed a biphasic tumor predominantly composed of solid nests of poorly differentiated cells, with a peripheral focus having a differentiated adenoid-cystic carcinoma-like appearance. Immunohistochemical study showed diffuse p16 positivity, and the specimen was reflexed to HPV genotyping. Polymerase chain reaction (PCR) analysis was positive for the HPV 35 serotype. Margins of the resection were negative. Perineural invasion was not identified; however, lymphovascular invasion was present. The patient received no postoperative chemotherapy due to a history of renal transplant.

### Case 2
A 46-year-old patient presented with chief complaint of nasal obstruction. The patient received multiple turbinate injections with some relief; however, a polypoid mass from the posterior right aspect of the inferior turbinate was visualized upon further inspection. Subsequent computed tomography imaging revealed a polyp at the left maxillary sinus. Positron emission tomography (PET) scan showed slight avidity at the right inferior turbinate. The patient underwent a right medial maxillectomy and turbinate resection for the nasal cavity mass. Resection margins were negative for carcinoma, and final pathology of the right inferior turbinate mass was consistent with HPV-related carcinoma with ACC-like features.
The histologic findings included a prominent basaloid cell proliferation with an associated identifiable ductal component. The specimen was sent for HPV genotyping via PCR and was positive for HPV 33. As with patient 1, there was no evidence of perineural invasion observed.

**Histology**

Microscopically, both cases demonstrated a highly cellular proliferation of basaloid cells. The cells exhibit hyperchromatic, angulated nuclei with scant cytoplasm, and a high nuclear to cytoplasmic ratio. The growth pattern of case 2 was predominantly solid (Fig. 1). Case 1 was dominated by a lobular pattern consisting of nests, many with central necrosis, surrounded by fibrous septa (Fig. 2). Case 1 exhibited frequent areas with peripheral palisading of the cells at the borders of these nests. Both carcinomas exhibited cribriform and tubular architecture in addition to the more lobular and solid areas (Fig. 3). Within the microcystic spaces of the cribriform areas was a basophilic material resembling the intracystic material seen in adenoid cystic carcinoma. Ductal cells could also be identified at the center of the lobules, with occasional duct formation (Fig. 4). Additionally, both cases exhibited surface epithelial dysplasia (Fig. 5).

Immunohistochemically, both tumors had some reactivity with cytokeratins. Both tumors expressed positivity for myoepithelial markers. Case 1 had patchy smooth muscle actin and S100 positivity, whereas case 2 had diffuse, strong positivity for p63, S100, and smooth muscle actin. Both were positive for CD117, and both were strongly and diffusely positive for p16. Both cases were sequenced to determine the HPV genotype.

**DISCUSSION**

Although the association between HPV and squamous cell carcinoma of the oropharynx is well established...
in the head and neck literature, HPV also plays a causative role in the development of the sinonasal tract malignancies. In fact, HPV may be the most significant causative agent implicated in sinonasal tumorigenesis and is implicated in as many as 21% of sinonasal carcinomas. Other than HPV, occupational exposures such as wood dust are among the few etiologic agents found to be associated with carcinoma of the sinonasal tract. However, risk factors for development of sinonasal carcinoma are controversial, and unlike oropharyngeal cancer, tobacco smoking is not considered a prominent etiologic agent in the development of sinonasal tract malignancy. On the whole, sinonasal carcinoma appears to have an increased prevalence in Caucasians, confers a relatively low 5-year disease-specific survival (53.7%), and most commonly presents as squamous cell carcinoma (41.9%). Interestingly, in HPV-related carcinoma with ACC-like features, the microcystic spaces, vague tumor spindling, and biphasic tumor cells more closely resemble salivary gland carcinoma than conventional HPV-related squamous cell carcinoma.

Research into HPV-related carcinoma with ACC-like features is still in its infancy. When evaluating the relationship between ACC, HPV, and p16 overexpression, Boland et al. discovered two cases of high grade ACC that tested positive for the presence of HPV. Subsequently, a total of 14 cases described by Bishop et al. further characterized this oncologic variant, suggesting that it confers a better prognosis than adenoid-cystic carcinoma. At this time, no cases to date have documented regional or distant metastasis, and surgical management alone has proven sufficient in the past. In our study, both patients were successfully treated with surgical resection, did not receive postoperative radiotherapy, and have been followed with serial imaging with no recurrences to date. As such, we advocate for careful observation and serial imaging following surgical resection to obviate the need for unnecessary and potentially harmful adjuvant radiotherapy. Still, the number of documented cases and available follow-up data is considered insufficient to determine the exact biological behavior of this carcinoma.

The first series published by Bishop et al. describes this novel subset of HPV-related sinonasal carcinoma as characterized by adenoid cystic-like features but distinctly not an adenoid cystic carcinoma. Although this newly discovered oncologic phenotype of the sinonasal tract demonstrates a significant morphologic overlap with ACC, it is distinguished by its association with HPV and specific histologic characteristics. In contrast to classical adenoid cystic carcinoma, HPV-related carcinoma with ACC-like features is typically limited to the sinonasal tract, lacks MYB:NFIB gene translocations, and demonstrates associated dysplasia or carcinoma in situ of the overlying surface epithelium (see Fig. 5). Interestingly, most cases show the uncommon HPV 33 as the predominant viral serotype. Less common serotypes such as HPV 35, as in our case, and HPV 56 have been identified as well. As we continue to uncover diverse sinonasal neoplasm subtypes, an understanding of the relationship between virus and tumor entity becomes more important in the search for new therapeutic targets and prognostic indicators.

CONCLUSION

We here report one of the first prospective case series of HPV-related carcinoma with adenoid cystic-like features. To date, surgery has proven itself to be an effective treatment modality, but long-term follow-up, in addition to greater sample sizes, are necessary to better characterize the clinicopathological significance of this new oncologic subtype.

BIBLIOGRAPHY