Human Papillomavirus–Related Carcinoma With Adenoid Cystic–like Features of the Sinonasal Tract (Also Known as Human Papillomavirus–Related Multiphenotypic Sinonasal Carcinoma)

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• Human papillomavirus (HPV)–related carcinoma with adenoid cystic–like features is a rare, recently recognized entity restricted to the sinonasal tract. By definition, it is associated with high-risk HPV infection, particularly with HPV type 33. In most cases, tumors are composed of dual cell populations, including predominant basaloid myoepithelial cells and usually inconspicuous ductal cells. Solid components with focal cribriform or tubular patterns, abrupt keratinization within tumor nests, and squamous dysplasia of the surface epithelium are characteristics of HPV-related carcinoma with adenoid cystic–like features. The immunohistochemistry of p16 followed by high-risk HPV testing may help in the differential diagnosis. Recent studies have demonstrated that the morphologic features of this entity are more diverse than initially believed. Surgical resection is the prime alternative for treatment. According to the limited data, the prognosis of this disease may be better than that of other sinonasal carcinomas.

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Human papillomavirus (HPV) is known to play a critical role in the oncogenic process of several human tumors, including squamous cell carcinoma of the cervix and a subset of carcinomas of the head and neck. Human papillomavirus–related carcinomas of the head and neck are frequently found in the oropharyngeal area and generally have a nonkeratinizing squamous morphology. A recent study also demonstrated that HPV type 16 is responsible for up to 80% of oropharyngeal carcinomas.[1] Approximately 20% to 25% of the sinonasal carcinomas harbor transcriptionally active HPV, but whether HPV positivity is associated with improved clinical outcomes and represents a distinct group of lesions is unclear.[2,3] Among them, HPV-related carcinoma with adenoid cystic–like features, a recently proposed disease, has attracted much attention in recent years.

Human papillomavirus–related carcinoma with adenoid cystic–like features was first described in 4 peculiar cases with a morphology resembling adenoid cystic carcinoma (AdCC) in several aspects in a series of high-risk HPV-positive sinonasal tract carcinomas.[2] Bishop et al[4] then proposed it as a new entity; only 20 cases had been reported in the English literature before the series of 49 cases recently described by Bishop et al.[4–8] In the latest World Health Organization classification of head and neck tumors, HPV-related carcinoma with adenoid cystic–like features is recognized as a provisional disease under the category of nonkeratinizing squamous cell carcinomas. Because of its rarity, little is known about its morphologic spectrum, possible diagnostic challenges, optimal therapy, and the long-term follow-up for this entity. Here we review the current state of knowledge of HPV-related carcinoma with adenoid cystic–like features.

CLINICAL FEATURES

Human papillomavirus–related carcinoma with adenoid cystic–like features is a tumor restricted to the sinonasal area and is more common in women than in men. No specific race predisposition or definite link to cigarette smoking is established. The age at diagnosis reported for patients with these tumors ranges from 28 to 90 years, and the clinical presentation includes nasal obstruction, stenosis, sinusitis, epistaxis, pain, epiphora, and exophthalmos. The nasal cavity, paranasal sinuses, middle turbinate, and nasal septum are the most common sites of occurrence of HPV-related carcinoma. However, the involvement of the inferior turbinate, lacrimal duct, cranial fossa, and the orbit has also been reported.[5,7] Table 1 summarizes the clinicopathologic features available in the current literature on HPV-related carcinoma with adenoid cystic–like features.

PATHOLOGIC FINDINGS

Morphologically, a predominant population of basaloid myoepithelial-type cells and scattered ductal cells (Figure 1, A and B) characterizes HPV-related carcinoma with adenoid

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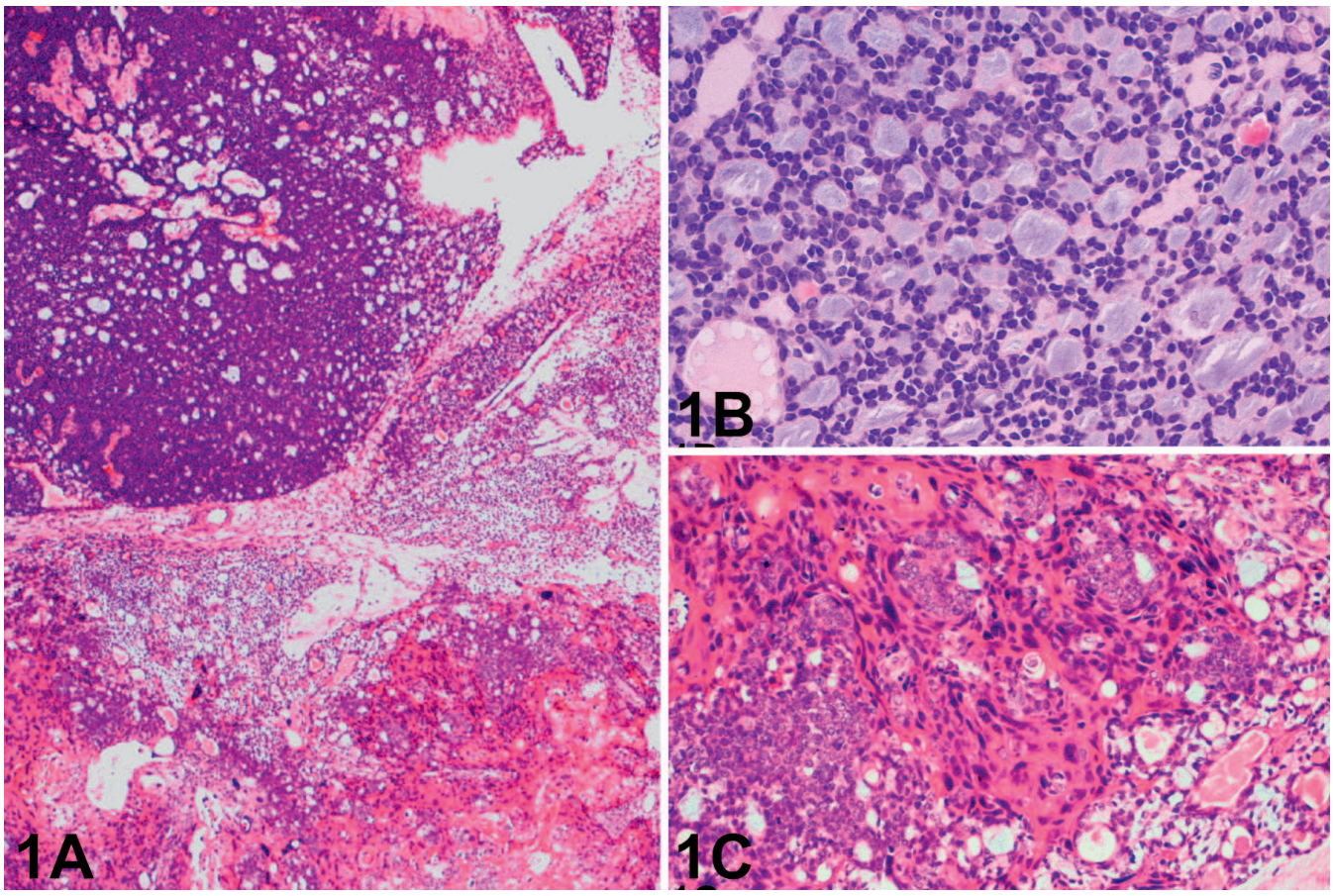

Figure 1. *A, In a low-power field, human papillomavirus (HPV)–related carcinoma with adenoid cystic–like features is usually composed of predominant basaloid cells arranged in solid or cribriform patterns. Abrupt keratinization within tumor nests is characteristic. B, A dual population including basaloid myoepithelial cells and inconspicuous ductal cells is typical of HPV-related carcinoma with adenoid cystic–like features. C, Abrupt keratinization within tumor nests (hematoxylin-eosin, original magnifications ×40 [A], ×400 [B], and ×200 [C]).*

cystic–like features. The basaloid myoepithelial-type cells bearing hyperchromatic, slightly angulated nuclei and having scant cytoplasm are usually arranged in a solid, tubular, or cribriform growth pattern. Microcystic spaces containing basophilic material are also present. The scattered ductal cells are cuboidal, with pale or eosinophilic cytoplasm and vesicular nuclei arranged as focal ductal structures surrounded by basaloid cells.[6,8] Cell spindling, cytoplasmic clearing, and plasmacytoid morphology have also been reported.[7] Lymphovascular invasion, although rare, has been demonstrated in a case report published in 2018.[9] Increased mitotic activity and tumor necrosis are common findings; however, nodal metastasis has not yet been identified.

Compared with AdCC, the presence of a solid pattern, focal squamous differentiation within the tumor (abrupt keratinization or scattered nonkeratinizing nests; Figure 1, C), squamous dysplasia of the surface epithelium, and tumor giant cells are more characteristic of HPV-related carcinoma with adenoid cystic–like features. In addition, the typical hyalinized tumor stroma of AdCC and bone invasion are less frequently observed in HPV-related carcinoma with adenoid cystic–like features.[8] One large case series including 49 cases of HPV-related carcinoma with adenoid cystic–like features also reported the presence of slitlike (or hemangiopericytoma-like) vessels, epithelial-myoepithelial carcinoma–like components, sarcomatoid differentiation, and heterologous elements (chondroid and osseous) in these tumors.

Because of the presence of multidirectional phenotypes, a more broader morphologic spectrum than initially appreciated, the minimal adenoid cystic–like components in some cases, and the strong association with high-risk HPV, Bishop et al[7] advocated that this group of tumors should be renamed HPV-related multiphenotypic sinonasal carcinoma.

ANCILLARY STUDIES

The immunohistochemical profile of HPV-related carcinoma with adenoid cystic–like features is similar to that of AdCC. Both ductal and basaloid cells are positive for cytokeratin (AE1/AE3), and the expression is stronger in the ductal cells than in the luminal basaloid cells (Figure 2, A).[4] Both ductal and basaloid cells are immunoreactive for SOX-10. The ductal cells typically express c-kit (CD117; Figure 2, B), and the basaloid cells typically express myoepithelial markers, such as S100, p63 (Figure 2, C), p40, calponin, and smooth muscle actin. Strong and diffuse p16 (Figure 2, D) immunoreactivity in both of the cells is consistently observed in HPV-related carcinoma with adenoid cystic–like features, but it is very rare in AdCC. The Ki-67 labeling index varied from 40% to 90%.

Table 1. Summary of the Current Literature on Human Papillomavirus (HPV)–Related Carcinoma With Adenoid Cystic–like Features

Source, y	No.	Age Range, y/Sex	Location	Squamous Dysplasia of the Surface Epithelium, No. (%)	Diffuse p16 Staining, No. (%)	HPV Genotypes (No.)	Follow-up
Bishop et al,[4] 2013	8	40–73/6 F, 2 M	Nasal cavity, paranasal sinus, orbit	6 (75)	8 (100)	33 (6), 35 (1), unknown (1)	NED: 4; LR: 2; NA: 2
Hwang et al,[5] 2015	1	75/F	Inferior turbinate	1 (100)	1 (100)	High-risk HPV	NED: 1
Andreasen et al,[6] 2017	6	29–60/4 F, 2 M	Nasal cavity, paranasal sinus, septum, middle turbinate	6 (100)	6 (100)	33 (3), 35 (2), 56 (1)	NED: 5; LR: 1
Hang et al,[8] 2017	5	30–58/0 F, 5 M	Nasal cavity, middle turbinate	4 (80)	5 (100)	33 (4), 16 (1)	NED: 4, NA: 1
Bishop et al,[7] 2017	49	28–90/28 F, 21 M	Nasal cavity, paranasal sinus, orbit, lacrimal duct, cranial fossa	34 (69)	49 (100)	High-risk HPV cocktail (49), 33 (33), 35 (3), 56 (1), 16 (1), unknown (1)	NED: 25; LR: 14; NA: 10
Shah et al,[19] 2018	1	69/F	Hard palate	1 (100)	1 (100)	33 (1)	NA:1

Abbreviations: LR, local recurrence; NA, not available; NED, no evidence of disease.

Table 2. Summary of the Morphologic Features and Ancillary Testing Helpful in Differential Diagnosis For Other Mimic Entities and Human Papillomavirus (HPV)–Related Carcinoma With Adenoid Cystic–like Features

	HPV-Related Carcinoma With Adenoid Cystic–like Features	Adenoid Cystic Carcinoma	Polymorphous Adenocarcinoma	Epithelial-Myoepithelial Carcinoma	Basal Cell Adenocarcinoma	Nonkeratinizing Squamous Cell Carcinoma
Cell population	2	2	1	2	2	1
Characteristic morphologic features	Solid and cribriform patterns	Tubular, cribriform, or solid patterns	Infiltrative growth with diverse patterns	Bilayered tubular, glandular, and solid patterns	Solid, trabecular, tubular, or membranous patterns	Solid pattern
	Predominant basaloid myoepithelial cells and scattered ductal cells	Luminal epithelial cells and myoepithelial cells	Uniformly round to polygonal or fusiform cells	Inner layer of epithelial cells, and outer layer of myoepithelial cells	Central large, polygonal cells, and peripheral small, basaloid cells	Smooth stromal interface (pushing border)
	Squamous dysplasia of surface epithelium	Hyalinized stroma	Blue-gray or hyalinized stroma	Cribriform pattern is typically absent	Peripheral nuclear palisading of tumor nests	Peripheral palisading may be present
	Rare lymphovascular invasion[9]	Basal lamina material within pseudocyst				
Squamous differentiation	Present	Rarely present[11,a]	May be present	May be present	May be present	Present
Ki-67 index	Higher (40%–90%)	Higher (>10%)			Low (<5%)	
Special studies	p16 positive[b]	*MYB*/*MYBL1* rearrangement	p63 positive and p40 negative	Dual population highlighted by epithelial and myoepithelial markers	β-catenin positive[c]	p16 positive if high-risk HPV related
	Associated with high-risk HPV infection	Rarely associated with HPV infection[10–12]			Cytokeratin 5/6 and bcl-2 positive	

[a] Squamous metaplasia of nasopharyngeal adenoid cystic carcinoma (3 of 86 patients) has been reported in a large series published by Thompson et al[11] in 2014.
[b] p16 positivity is defined by >75% nuclear and cytoplasmic stain in the tumor cells.
[c] β-catenin positivity is defined by diffusely nuclear stain in the tumor cells.

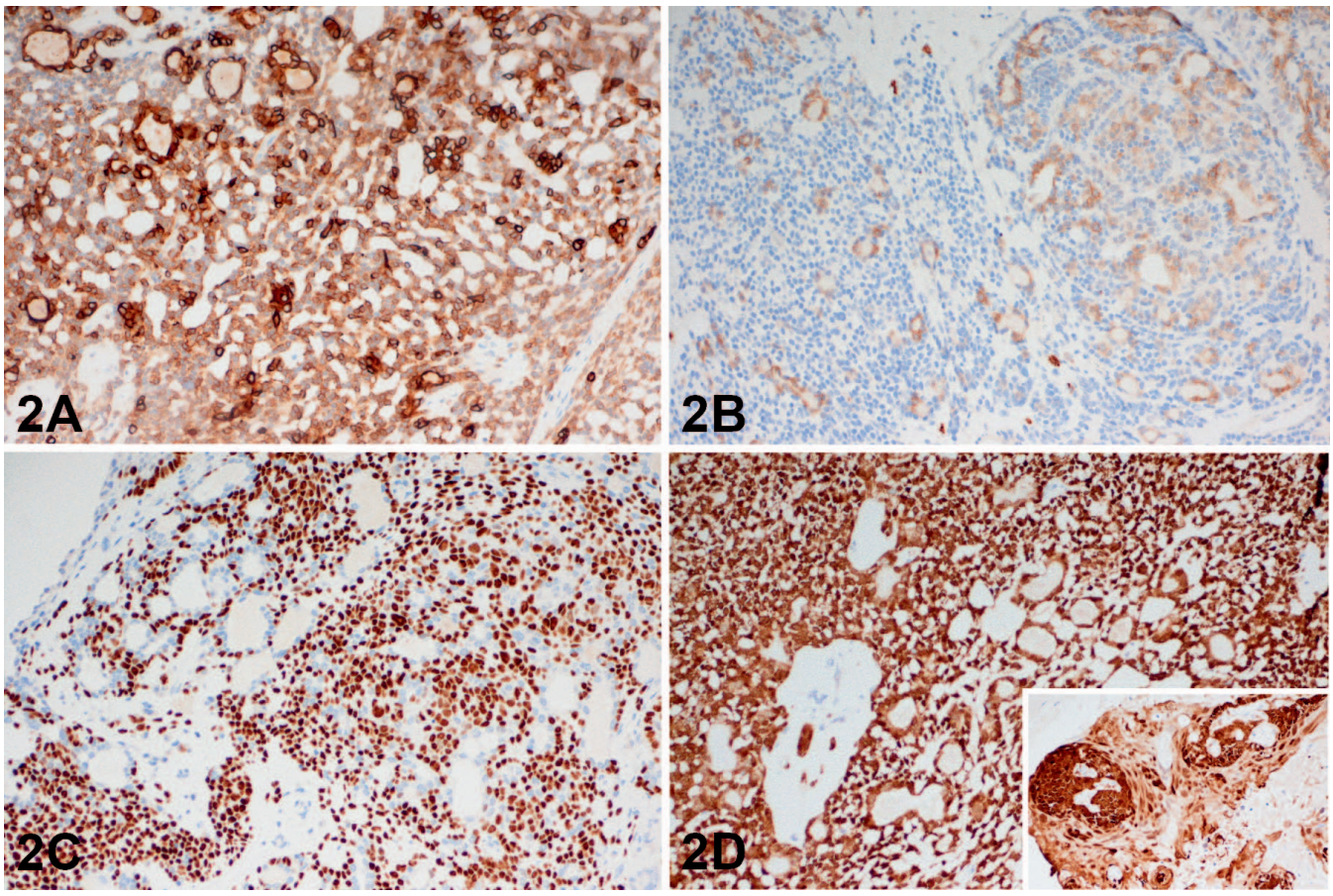

Figure 2. *A, Positive cytokeratin (AE1/AE3) immunostaining is visible in both ductal and basaloid cells but is stronger in the ductal cells. B, The c-kit (CD117) immunostaining typically highlights ductal cells. C, Basaloid myoepithelial cells are immunoreactive for p63, but ductal cells are negative. D, Strong and diffuse p16 immunoreactivity is present in both ductal cells and myoepithelial cells. In addition, the cells with squamous differentiation (inset) also show strong and diffuse p16 immunoreactivity (original magnification ×200).*

HPV PHENOTYPING

In contrast to sinonasal adenoid cystic carcinoma, which is rarely associated with HPV infection,[10–12] HPV-related carcinoma with adenoid cystic–like features is by definition associated with high-risk HPV infection, with a focus on HPV type 33 (most common) and type 35.[4,5] Andreasen et al[6] reported 1 case with HPV type 56 infection, and Hang et al[8] later presented the first case with HPV type 16. Unlike HPV-related carcinoma arising from uterine cervix, where latent HPV infection may be seen in more than 10% of healthy women, HPV is rarely present in normal sinonasal mucosa. The relatively HPV-deprived environment in this location supports the causative role of HPVs in the carcinogenesis.[6]

Although some tumors with adenoid cystic differentiation in the genitourinary or gynecologic system have been reported previously, the definite association with HPV infection remains unclear.[13–15] In a case series published in 2016,[16] lower female genital tract tumors with adenoid cystic differentiation could be subdivided into 2 groups: carcinoma with mixed differentiation including the adenoid cystic component, and pure adenoid cystic carcinoma. The former shows diffuse p16 expression and is related to high-risk HPV, and the latter shows the opposite results, which indicates that they may be 2 distinct entities. More studies are needed to clarify the relationship between the HPV infection and carcinoma with adenoid cystic–like features in different anatomic sites of the human body.

DIFFERENTIAL DIAGNOSIS

The main differential diagnosis for HPV-related carcinoma with adenoid cystic–like features includes some salivary gland tumors, particularly AdCC and nonkeratinizing squamous cell carcinoma. Some morphologic features and ancillary testing that may be helpful in the differential diagnosis are summarized in Table 2.

Besides the differences in morphologic features between HPV-related carcinoma with adenoid cystic–like features and AdCC mentioned above, p16 and MYB immunostaining followed by high-risk HPV testing and MYB/MYBL1 fluorescent in situ hybridization may be an appropriate strategy for further differential diagnosis in some equivocal cases.[6,8]

The presence of a dual cell population comprising both ductal and myoepithelial cells in HPV-related carcinoma with adenoid cystic–like features can help to rule out nonkeratinizing squamous cell carcinoma, myoepithelial carcinoma, and polymorphous adenocarcinoma. Most basal cell adenocarcinomas have at least focal peripheral palisading, a low mitotic rate, and a low Ki-67 labeling index (mostly <5%), and display diffuse nuclear staining of β-catenin[17]; HPV-related carcinoma with adenoid cystic–like features generally shows the opposite results. In some

situations, epithelial-myoepithelial carcinomas may be included in the differential diagnosis, but a cribriform pattern is typically absent in epithelial-myoepithelial carcinomas, except for the apocrine variant.[18] If the sarcomatoid and heterologous elements are predominant, it may be difficult to differentiate HPV-related carcinoma with adenoid cystic–like features from carcinosarcoma or carcinoma ex pleomorphic adenoma. More studies focusing on the relationship between HPV infection and these tumors are required for accurate diagnosis of this condition.

As stated by Bishop et al,[7] HPV-related carcinoma with adenoid cystic–like features should be considered in cases of a tumor containing high-grade salivary gland–like features that are difficult to assign to a specific category.

TREATMENT AND PROGNOSIS

To date, no gold standard or consensus treatment for HPV-related carcinoma with adenoid cystic–like features has been established. Most patients are surgically treated with or without adjuvant chemotherapy or radiotherapy. In a recent case series, it has been stated that about 36% of the patients developed local recurrences, and 2 of the 49 patients (5%) developed distant metastases in the lung and finger following surgery. This situation of distant metastases had not been previously reported. Although 43% of the patients in that series presented with advanced tumor stage, none of them developed lymph node metastasis or died of their disease, which may indicate a relatively indolent clinical behavior compared with other sinonasal carcinomas. However, the potential for very late local recurrence was emphasized by a case with a 30-year disease-free interval.[19]

CONCLUSIONS

Human papillomavirus–related carcinoma with adenoid cystic-like features is a rare entity in the sinonasal area, and it is more common in female than in male individuals, with a wide age range. Although recent studies have extended the morphologic spectrum of this entity, diffuse and strong nuclear as well as cytoplasmic staining for p16 and the association with high-risk HPV infection are unique. Squamous dysplasia of the epithelium and abrupt keratinization within tumor nests are helpful for the differential diagnosis. More studies including large cohorts and long-term follow-up are required to better understand the clinical nature of this entity.

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