The Sinonasal Tract: Another Potential “Hot Spot” for Carcinomas with Transcriptionally-Active Human Papillomavirus

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Abstract While high risk human papillomavirus (HPV) is well established as causative and clinically important for squamous cell carcinoma (SCC) of the oropharynx, its role in non-oro-pharyngeal head and neck SCC is much less clearly elucidated. In the sinonasal region, in particular, although it is a relatively uncommon site for SCC, as many as 20 % of SCC harbor transcriptionally-active high risk HPV. These tumors almost always have a nonkeratinizing morphology and may have a better prognosis. In addition, specific variants of SCC as well as other rare carcinoma types, when arising in the sinonasal tract, can harbor transcriptionally-active HPV. This article reviews the

current literature on HPV in sinonasal carcinomas, attempts to more clearly demonstrate what tumors have it and how this relates to possible precursor lesions like inverted papilloma, and discusses the possible clinical ramifications of the presence of the virus.

Keywords Human papillomavirus · Sinonasal · Nonkeratinizing · Squamous cell carcinoma · p16

Introduction

Human papillomavirus (HPV) associated oropharyngeal squamous cell carcinoma (SCC) is a distinct clinicopathologic entity [1] with improved prognosis. HPV DNA is

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Fig. 1 Inverted papilloma with synchronous squamous cell carcinoma. **a** Low power view showing an area of papilloma (*left side*) with polypoid tissue fragments lined by markedly thickened epithelium and having a central edematous and vascular stroma. This inverted papilloma has extensive squamous metaplasia. The invasive carcinoma (*right side*) is present as irregular and angulated nests of more basophilic tumor (40× magnification). **b** Medium power view showing areas of inverted papilloma immediately adjacent to invasive squamous cell carcinoma which is poorly differentiated with solid, irregularly shaped nests of cells with scant amounts of eosinophilic cytoplasm (100× magnification). **c** High power view of the squamous cell carcinoma showing the high nuclear to cytoplasmic ratios and oval to irregular, hyperchromatic and pleomorphic nuclei (400× magnification)

nuclear and cytoplasmic expression of p16 [7]. Amongst head and neck anatomic subsites, this occurs most frequently in the oropharynx [8], at a rate of up to 80 % in the current era [1, 9–11, 4, 12]. These patients have different risk profiles than traditional head and neck cancer patients, with a much larger fraction of non-smokers, lower overall smoke exposure, slightly younger age, and higher sexual (and particularly oral sex) exposure rates [7, 13]. Tumors are clinically, biologically, and molecularly distinct [14], and they have much better treatment response and better prognosis, as has been clearly established by large numbers of retrospective [7, 15] and prospective studies [16].

Although not widely recognized, transcriptionally-active HPV can be found in other head and neck subsites in more than just isolated carcinoma cases. Emerging data suggests that it is present in as many as 15–20 % of Epstein-Barr virus negative nasopharyngeal carcinomas [17, 18, 19]. Another potential “hot spot” for transcriptionally-active HPV-related carcinomas, it turns out, is the sinonasal tract [20, 21]. This article presents the current knowledge on HPV in sinonasal carcinomas and discusses the potential biology and clinical implications of the virus in such tumors.

Discussion

Overview of Sinonasal Carcinomas

The sinonasal tract (paranasal sinuses and nasal cavity) is, among head and neck anatomic subsites, a less common site for carcinoma development, particularly for SCC. Only about 3 % of all carcinomas of the upper aerodigestive tract arise here [22]. The diversity of carcinoma types, however, is as broad as any of the anatomic subsites. The proportion of SCC among all carcinomas is the lowest in the sinonasal region (approximately 65 %) relative to all other head and neck anatomic subsites [23, 24], and the rate of sinonasal SCC appears to be slowly decreasing [25]. Other sinonasal tumors include salivary gland carcinomas, non-salivary adenocarcinomas (intestinal and non-intestinal

frequently detected in head and neck SCC across all anatomic subsites, particularly when assessed by PCR [2]. However, to have clinical relevance, the HPV must be transcriptionally-active [1, 3]. This is established either by direct detection of high risk HPV E6 and E7 mRNA in tumors by RT-PCR [4, 5, 6] or by detection of HPV DNA by PCR or in situ hybridization combined with extensive

types), sinonasal undifferentiated carcinomas, neuroendocrine carcinomas, and rarer entities such as the recently described “adenoid cystic carcinoma like” carcinoma. Given the relatively uncommon incidence of sinonasal carcinomas (particularly relative to the oropharynx), the HPV “story” in sinonasal tract tumors has largely occurred under the radar, even among head and neck clinicians and pathologists.

HPV in Schneiderian Papillomas

While the majority of sinonasal SCC arise seemingly *de novo*, it is well established that Schneiderian papillomas, particularly inverted papillomas, are a significant risk factor for the development of SCC. As such, it is reasonable to begin the discussion with these neoplasms. Published rates of SCC in inverted papillomas range from 2 to 27 % in the literature, but in a collective review by Barnes in 2002 of 1,390 patients with inverted papilloma, 11 % were complicated by carcinoma development [26], while a more recent non-referral center review shows about 8 % (Thompson, unpublished data). The majority were synchronous (carcinoma present at primary presentation) and about 30 % metachronous (carcinoma developing after initial detection and treatment of the papilloma) (Fig. 1). The vast majority of these carcinomas are SCC, but mucoepidermoid, verrucous, spindle cell, sinonasal undifferentiated, and adenocarcinomas have been reported [26]. The amount of carcinoma varies greatly, from very focal to extensive, and this should be reflected in the pathology report. Oncocytic papillomas are much less common than the inverted type, but these are also at risk of carcinoma development, with between 4 and 17 % associated with carcinoma. These, again, are mostly SCC [26, 27].

Although the association between inverted and oncocytic Schneiderian papillomas and carcinoma sounds straightforward, it is not. Who gets carcinoma and why? There is particular confusion regarding the role of HPV in tumor development. The vast majority of studies have looked for HPV in inverted papillomas by DNA-based PCR. In a recent critical analysis of the literature, Lawson et al. [28] showed that HPV DNA (of any type—low or high risk) was present in approximately 20–25 % of inverted papillomas. HPV was more common in recurrent papillomas and those with dysplasia or frank carcinoma. HPV (of any type) was present in 22.3 % of papillomas without dysplasia or carcinoma, 55.8 % with high grade dysplasia, and 55.1 % with frankly invasive SCC. The ratio of low risk to high risk HPV was also skewed for papillomas with dysplasia or carcinoma. It was 4.8–1 with inverted papillomas without dysplasia or carcinoma, 1.1–1 with severe dysplasia, and 1–2.4 with frank SCC. Summarizing their results, high risk HPV is present in a

minority of inverted papillomas. Across such a large time period and breadth of studies, this association appears to be biologically important. Further, the development of subsequent dysplasia and carcinoma are strongly related to its presence [28]. HPV is distinctly uncommon in oncocytic papillomas (with many studies not detecting it) [26, 29], and, when found, is not clearly transcriptionally active. Exophytic papillomas, although they frequently harbor low risk HPV, almost always lack high risk HPV [26, 30].

Few papers have looked for HPV in “transcriptionally-active” form in inverted papillomas, and none have evaluated directly for HPV mRNA. p16 immunohistochemistry, a surrogate marker of transcriptional activity for high risk HPV, has been assessed in a few studies. These studies have shown mixed results [31], but suggest that p16 is expressed at low levels in most inverted papillomas [32], regardless of HPV DNA status, and that none have diffuse, intense staining [33].

HPV in Non-Papilloma-Related Squamous Cell Carcinomas

Syrjanen et al. [34] performed a large meta analysis of HPV in sinonasal carcinomas, regardless of type or precursor lesion, and found an overall incidence of ~30 %, by various DNA detection methods. Lawson et al. [28], in addition to analyzing HPV rates in papilloma-associated carcinomas, also examined studies of SCC not associated with inverted papilloma. They found HPV DNA by PCR in 46 of 230 (20.0 %) cases in the literature, much lower than the rate for SCC associated with inverted papilloma (55.1 %). More broadly, several studies have examined not only for HPV DNA, but have also reported morphology, ancillary markers like p16, and clinical outcomes [20, 21, 35]. Presumably these studies are identifying “transcriptionally-active” HPV (although no studies to date have directly assessed sinonasal SCC for high risk HPV mRNA).

The morphologic terms utilized in these studies for the SCCs have been based on the WHO Classification. To review the history, sinonasal nonkeratinizing SCC has also previously been known as “cylindrical” cell, “transitional” cell, and “Schneiderian” carcinoma. The name cylindrical cell carcinoma was first coined by Ringertz in 1938 [36] and was recommended as the preferred term by Shanmugaratnam in the WHO classification of 1991 [37]. Microscopically, the prototypical “cylindrical” cell carcinoma is composed of papillary fronds and thick ribbons of cells that quite often connect to the surface epithelium giving rise to invaginations, which at low magnification may mimic the growth pattern of inverted papilloma. The tumor cells are commonly cylindrical and have tendency to palisade with the cells perpendicular to the underlying basement membrane. The nuclei are atypical and show

Fig. 2 Nonkeratinizing squamous cell carcinoma of the sinonasal tract. **a** Low power H&E showing rounded nests of *blue* tumor with smooth edges and little to no stromal reaction (40× magnification). **b** Higher power H&E showing a rounded tumor nests consisting of *blue* cells with modest amounts of cytoplasm and oval, hyperchromatic

nuclei. There is central necrosis (200× magnification). This tumor was positive for both p16 and high risk HPV by DNA in situ hybridization. (Images courtesy of Justin A. Bishop, M.D., Johns Hopkins University Department of Pathology; *HPV* human papillomavirus)

abundant mitotic activity with abnormal mitotic figures and brisk apoptosis. The pattern of invasion is usually pushing, being characterized by smooth margins with focal infiltration of the stroma. The basement membrane remains in most cases conspicuous, despite stromal infiltration and this should not be regarded as carcinoma in situ. Foci of squamous metaplasia, with transition from the more cylindrical appearing nests to frank squamous differentiation are common, and in recent years, it has become clear that these tumors are probably indistinguishable from nonkeratinizing SCC, which is term put forth by the 2005 WHO classification of head and neck tumors [38]. Designations such as “transitional cell carcinoma” and “Schneiderian” carcinoma are confusing at present and should not be used. The term transitional cell carcinoma was primarily used for tumors of the urinary tract (now generally discarded in favor of “urothelial”) and the broad term “Schneiderian” applies to all tumors derived from sinonasal respiratory “Schneiderian” epithelium.

Nonkeratinizing sinonasal SCC is very similar in morphology to its counterpart in the oropharynx [20, 21, 35], consisting of a “blue cell” tumor with predominantly basaloid-appearing tumor cells in large, rounded nests or ribbons with smooth, often well demarcated, borders. As mentioned, there is often central necrosis with prominent mitoses and apoptosis (Fig. 2). Keratinizing SCC, on the other hand, is morphologically identical to “conventional” SCC at all other head and neck subsites.

El-Mofty et al. [35] reported 29 cases, of which 21 were conventional, keratinizing-type SCC and 8 nonkeratinizing SCC. HPV DNA was detected by PCR in 4 of 21 (19.0 %) keratinizing SCC and 4 of 8 (50.0 %) nonkeratinizing SCC. p16 immunohistochemistry was strong and diffuse in only 1 of 21 (4.8 %) keratinizing SCC but was strong and diffuse in 5 of 8 (62.5 %) of the nonkeratinizing SCC. All 4

Table 1 Transcriptionally-active high risk HPV rates* by histologic type of sinonasal carcinoma across current literature

Histologic type	HPV positive (%)
Non-keratinizing SCC	25/63 (39.7)
Keratinizing SCC	3/88 (3.4)
Basaloid SCC	5/12 (41.7)
Papillary SCC	6/8 (75.0)
Adenosquamous carcinoma	6/9 (66.6)
Spindle cell carcinoma	0/3 (0)
Small cell carcinoma	1/6 (16.7)
Sinonasal undifferentiated carcinoma	2/31 (6.5)

* Defined as either detectable high risk HPV E6/E7 mRNA or as combined diffuse p16 expression with detectable high risk HPV DNA
HPV human papillomavirus, *SCC* squamous cell carcinoma

HPV DNA positive nonkeratinizing SCC were p16 positive, as was one keratinizing SCC. Bishop et al. [21] analyzed a tissue microarray of 178 sinonasal carcinomas with p16 immunohistochemistry and high risk HPV by DNA in situ hybridization, and found 35 of 178 (20.0 %) cases to be positive for both. Among the 44 tumors described as nonkeratinizing SCC, 15 (34 %) were HPV DNA and p16 immunohistochemistry positive. All 25 keratinizing SCC were negative. Alos et al. [20] studied 60 patients with sinonasal SCC. Of these, 42 were keratinizing-type and 11 nonkeratinizing. HPV DNA was present in 12 of 60 (20.0 %) tumors overall including 6 of 11 (54.6 %) nonkeratinizing SCC and only 2 of 42 (4.8 %) keratinizing SCC. All of the HPV positive tumors were diffusely positive for p16, regardless of histologic type. Finally, a very recent study by Takahashi et al. [39] studied 70 sinonasal SCC for prognostic markers. They utilized DNA in situ hybridization and p16 immunohistochemistry but did not describe the SCC morphology/subtypes. They

found only 6 of 64 (9.4 %) cases to be positive for high risk HPV. There were 12 p16 positive patients, including 5 of the 6 HPV DNA positive patients. So for “transcriptionally-active” HPV, only 5 of 64 (7.8 %) informative sinonasal SCC cases were positive [39].

Summarizing all of these four studies (Table 1), with the definition of “transcriptionally-active HPV” as tumors with both positive p16 immunohistochemistry and positive high risk HPV DNA (either by PCR or in situ hybridization), 33 of the 215 (15.3 %) SCC were positive [20, 21, 35]. This is a lower rate than for oropharyngeal SCC but higher than for oral cavity, laryngeal, and hypopharyngeal SCCs, making the sinonasal tract a possible “hot spot” for transcriptionally-active HPV-related tumors.

The Alos et al. [20] study of 60 patients was the first to report on patient outcomes based on HPV status. The 12 (20 %) p16 and HPV DNA positive patients had similar age, gender distribution, and tumor stages, but significantly lower smoking exposure, and showed statistically significantly better progression free and overall survival in multivariate analysis [20]. The study by Bishop et al. [21] included 91 patients with sinonasal SCC, 28 (31 %) of whom were HPV DNA and p16 positive. They showed a strong trend towards improved overall survival in the HPV positive patients (hazard ratio for HPV negative patients relative to positive of 1.80, 95 % CI 0.74–4.38), but this was not statistically significant ($p = 0.19$). A recent study by Takahashi et al. [39] of 70 patients did not find any significant difference in survival by HPV status, although their number of HPV/p16 positive patients (5 total) was small, limiting any real conclusion from their data.

HPV in Squamous Cell Carcinomas Arising from Inverted Papilloma

Interestingly, even though many inverted papillomas have high risk HPV DNA by PCR and >50 % of SCC arising in inverted papilloma have it, the vast majority of SCC with transcriptionally-active HPV in them have not arisen in the clinical context of a papilloma. In the study by Alos et al. [20], for example, of their 12 SCC patients who had previous inverted papilloma, only one (8.3 %) tumor had transcriptionally-active HPV. However, of their 48 transcriptionally-active HPV negative SCC patients, 11 (22.9 %) had prior inverted papilloma. Further, almost all SCC arising from inverted papilloma are keratinizing in morphology, rather than nonkeratinizing [20]. As previously mentioned, it is the nonkeratinizing morphology that correlates with transcriptionally-active HPV (~40 %), while it is rare in keratinizing SCC (~5 %) [20, 21, 35]. In the Bishop et al. series, only 1 of their 16 patients with SCC arising with/from inverted papilloma had transcriptionally active HPV. These findings suggest that, although perhaps

paradoxical, even though HPV is associated with inverted papilloma pathobiology and with SCC development, the established SCCs that arise out of these lesions do not seem to retain, nor are they biologically driven by, transcriptionally-active virus.

HPV in Specific Squamous Cell Carcinoma Histologic Variants

Transcriptionally-active HPV has also been reported in many of the histologic SCC variants when they arise in the sinonasal region (Table 1). In fact, more than half of the cases of sinonasal papillary SCC [20, 40, 21] and adeno-squamous carcinoma [41, 21] in the literature that were tested for HPV DNA or RNA and for p16 immunohistochemistry have been HPV positive. Almost half of basaloid SCC [20, 42] are positive as well. One would suspect that the prognosis of these tumors with transcriptionally-active HPV would be better, but there are simply not sufficient cases evaluated to make any meaningful assessment.

HPV in Other Sinonasal Carcinomas

There is little data regarding HPV in non-squamous sinonasal carcinomas, but it nevertheless remains compelling (Table 1). Most sinonasal undifferentiated carcinomas lack HPV DNA, although rare positive cases have been reported [35, 43]. While p16 expression is a good surrogate marker for transcriptionally-active HPV in general, it must not be relied upon alone in sinonasal tumors, as sinonasal undifferentiated carcinoma (and some other types such as small cell carcinoma and adenoid cystic carcinoma [44]), have been reported to express it extensively even when not associated with transcriptionally-active HPV [43, 21]. Small cell (high grade neuroendocrine) carcinomas are another uncommon type of sinonasal carcinoma, many of which overexpress p16 by immunohistochemistry independent of HPV status. Only 1 of 6 sinonasal neuroendocrine carcinomas assessed for HPV DNA and p16 was positive for both [21].

The knowledge regarding HPV in other carcinomas, such as salivary gland tumors, is just emerging. Across head and neck sites, high risk HPV has been reported in some cases of salivary carcinoma such as mucoepidermoid carcinoma [45], but this has yet to be confirmed by other groups. This study mentions oral, oropharyngeal, and major salivary gland subsites, but it is not clear if any of these cases were sinonasal. Boland et al. [44] examined adenoid cystic carcinomas across the entire head and neck region and found 2 of 27 (7.4 %) to be HPV DNA positive by in situ hybridization. Both were diffusely p16 positive, and both were high grade and centered in the sinonasal

Fig. 3 HPV-related sinonasal carcinoma with adenoid cystic-like features. **a** H&E showing a basaloid neoplasm with regular, cribriform spaces with basophilic stromal material, giving it a striking resemblance to true adenoid cystic carcinoma (200× magnification). **b** p16 immunohistochemistry showing strong, diffuse,

nuclear and cytoplasmic staining (200× magnification). **c** DNA in situ hybridization which is positive with granular, basophilic nuclear staining in the tumor cells (400× magnification). *HPV* human papillomavirus

Fig. 4 True adenoid cystic carcinoma of the sinonasal tract. **a** H&E showing a basaloid tumor with cribriform nests having basophilic ground substance in many of the rounded, duct-like spaces. However, there are foci of true duct formation with open lumina as indicated by arrows (100× magnification). **b** p16 immunoreactivity is selectively associated with the cells lining true ductal structures (200× magnification)

tract. Shortly, thereafter, Bishop et al. [46] also reported five HPV DNA positive sinonasal carcinomas with a striking resemblance to adenoid cystic carcinoma. They went on to describe (and thoroughly characterize) a larger cohort of 8 patients with these tumors. While very much resembling adenoid cystic carcinoma, characterized by solid and/or cribriform lobules of basaloid cells with peripheral palisading around rigid, round, microcystic spaces with basophilic material resembling glycoaminoglycan and focal ductal formations (Fig. 3), 6 of their 8 tumors also had squamous dysplasia of the surrounding surface epithelium [46]. This latter feature is not in the spectrum of true adenoid cystic carcinoma. All cases showed patchy, but convincing, evidence of “myoepithelial” differentiation by immunohistochemistry, and all were positive for high risk HPV (types 33 or 35) by DNA in situ hybridization and/or PCR and strongly and diffusely positive for p16 [46]. This differs from the expression of p16 in conventional adenoid cystic carcinoma, which is commonly expressed, but selectively localized to the true luminal cells (Fig. 4) [47]. The authors termed these tumors “adenoid cystic-like carcinoma” and suggested that they may be a distinct type of sinonasal carcinoma [46]. In hindsight, the two “solid adenoid cystic carcinomas” reported by the earlier Boland et al. [44] study might have represented this entity as well. The presence of surface squamous dysplasia suggests to many that these tumors may correspond to adenosquamous carcinoma with a glandular component other than nonspecific adenocarcinoma, while to others, the presence of myoepithelial differentiation by p63, calponin, and smooth muscle actin staining suggests that they may more likely represent salivary gland tumors. The true nature of these rare and very unusual HPV-related tumors is yet to be clearly defined.

General Considerations

Overall, it appears that HPV is important for the pathogenesis and progression of many sinonasal neoplasms, particularly inverted papillomas, SCCs, and less common carcinomas like the adenoid cystic-like carcinoma. Most of the HPV positive cases have evidence of transcriptional activity, and the majority of cases harbor HPV type 16 [35, 20], which is known to be the major high risk HPV type in other head and neck cancers that harbor biologically important high risk HPV. Many questions remain unanswered, however. It is not known how HPV is transmitted to the sinonasal tract. Patients with HPV-related oropharyngeal SCC have lower smoking rates and higher sexual exposure [7, 13]. It is quite clear that sexual transmission is the route of exposure to high risk HPV. Unlike oropharyngeal SCC, this route has not been established for sinonasal SCC. Further, the rate of oropharyngeal SCC has been increasing (up to 225 % increase in the past several decades) [48], whereas the rate of sinonasal SCC has been slowly decreasing [25]. This suggests different pathophysiology. The prognostic significance of HPV, when present in transcriptionally-active form, is still unclear for sinonasal SCC. It will take large, multi-institutional studies to address this question. When HPV-specific therapies are developed, however, this subset of tumors may be targetable. Further, if the HPV is really critical for the development and active growth of these sinonasal carcinomas, as it appears to be, then vaccination should be preventative for these tumors, just as with HPV-related cervical and oropharyngeal SCC.

Clinical Practice Recommendations

Given the findings regarding HPV and sinonasal carcinomas to date, what then are the ramifications for routine clinical practice? Given the low overall numbers of patients in the available studies and their largely retrospective nature and lack of homogeneity, limited recommendations can be made at this time. With regard to inverted papillomas, while a minority harbor high risk HPV and it is a risk factor for SCC development, this association is far from established and further, clinical management would not, and should not, be different by HPV status of these lesions. All of these tumors need resection and close clinical follow up. Although it may become part of routine practice in the future as more data is accumulated regarding long term outcomes and risk for transformation to carcinoma, at this time, routine HPV testing for these tumors is not indicated.

For sinonasal SCC, transcriptionally-active HPV is present almost exclusively in the nonkeratinizing type (~40 %). With the diagnosis of nonkeratinizing sinonasal SCC in routine practice, the limited amount of data suggesting a positive prognostic benefit of HPV currently is

not sufficient to recommend routine HPV or p16 testing of such tumors at this time. With the diagnosis of keratinizing SCC (~5 %), the rarity of transcriptionally-active HPV (~5 %) means that testing for HPV or p16 is not recommended. For the rare histologic variants of SCC and for other sinonasal carcinomas, with the exception of the newly described adenoid cystic-like carcinoma where there is a strong, almost definitional, link with HPV, there simply is not enough data to recommend HPV testing of them.

Summary

In summary, a significant minority of sinonasal SCC (~15–20 %) harbor transcriptionally-active HPV. These are usually nonkeratinizing, only rarely arise from a preexisting Schneiderian papilloma, and may have improved survival compared to HPV negative tumors, although the numbers of studies and patients are still small. High risk HPV may be important in the pathogenesis of inverted papilloma, and its presence appears to increase the risk of developing SCC. Despite this, the established tumors that arise from inverted papillomas are usually keratinizing type and lack transcriptionally-active HPV. Finally, many other less common sinonasal carcinomas can harbor transcriptionally-active HPV, and unique appearing newer entities such as the “HPV-related carcinoma with adenoid cystic-like features” may be defined by the virus itself. However, the clinical significance for tumors with transcriptionally-active HPV is still unclear and will have to be defined in future studies.

Conflict of interest The authors have no financial or other conflicts of interest to report.

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