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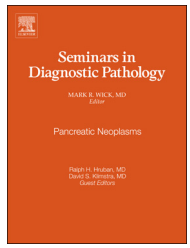

Human papillomavirus-associated neoplasms of the sinonasal tract and nasopharynx

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ABSTRACT

It is now well established that human papillomavirus (HPV) is an important causative factor in a subgroup of head and neck cancer. In the head and neck, while HPV is strongly associated with squamous cell carcinoma arising in the oropharynx, there is a growing interest in HPV-associated neoplasms of non-oropharyngeal origin including those which arise within sinonasal and nasopharyngeal mucosa. This article reviews current literature on the association of HPV with Scheiderian papillomas, sinonasal squamous cell carcinoma, sinonasal undifferentiated carcinoma, carcinoma with adenoid cystic-like features, and nasopharyngeal carcinoma. Several clinical implications of HPV detection in sinonasal and nasopharyngeal carcinomas are briefly discussed.

Introduction

Recent years have seen a surge of interest in human papillomavirus (HPV)-associated head and neck neoplasms amongst pathologists and the wider clinical community. This interest is largely centred on HPV-associated oropharyngeal squamous cell carcinoma (OpSCC) because of its rise in incidence to "epidemic" proportions.[1] HPV-associated OpSCC has particular clinico-demographic, histological, genetic, and prognostic features. Importantly, patients with HPV-associated OpSCC have significantly improved overall- and disease-specific survival outcome compared with site-matched HPV-negative controls.[2] These features have led some authorities to call for HPV-associated OpSCC to be classified as a distinct subtype of head and neck cancer in future international classifications.[3] Alongside the recognition of HPV-associated OpSCC as a distinct clinical entity, there is a growing body of evidence indicating that the virus is also associated with a subset of non-oropharyngeal head and neck cancers including some of those that arise from the mucosa and subjacent structures of the nasal cavity, paranasal sinuses and nasopharynx. However, HPV-associated sinonasal and nasopharyngeal neoplasms are still under-recognised and their clinical significance is poorly understood. This review summarises current knowledge of HPV-associated sinonasal and nasopharyngeal neoplasms. Detailed histological features of individual entities are beyond the scope of this review but are described elsewhere in this issue.

HPV testing

HPV types that affect mucosal sites are categorised according to their oncogenic potential as high-risk (HPV-16, -18, -31, -33,

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-35, -39, -45, -51, -52, -56, -58, and -59) or low-risk (HPV-6 and -11). The presence of viral DNA can be detected by polymerase chain reaction (PCR) using consensus or type-specific primers, or by DNA in situ hybridisation using type-specific or a cocktail of probes. However, in order to confirm that the presence of viral DNA is of biological relevance, it is necessary to demonstrate HPV transcriptional activity. Additionally, in high-risk HPV types, the expression of the viral oncoprotein E7 results in overexpression of the cyclin-dependent kinase inhibitor p16. The latter is a recognised surrogate marker for high-risk HPV in head and neck cancer.[4] It is important to note that diagnostic protocols for HPV testing in head and neck cancer are currently limited to OpSCC. Surrogate markers, detection thresholds and diagnostic algorithms are yet to be validated in sinonasal tract neoplasms and this has resulted in marked heterogeneity and lack of standardisation of HPV testing methods in these tumours.

Schneiderian papillomas

Since the first report of the association of HPV with sinonasal Schneiderian papillomas (SPs) in the early 1980s, there have been numerous studies evaluating the incidence of the virus in this disease. Despite this, there is still currently no definitive consensus as to the causative role of HPV in SPs. This is in part due to the wide variation in detection rates of HPV in this disease. The variation in incidence rates has in the past been attributed to the diversity of detection methods with some authorities suggesting that the use of PCR as a single modality test for HPV is likely to result in a high false-positive rate.[5] However, recent evaluation of the evidence indicates that histological papilloma type, rather than detection method or geographic origin of the study, explains the variation of incidence rates of HPV in SP.[6,7]

There is currently lack of unequivocal acceptance of HPV as a causative agent in SP for the following reasons:

(i) HPV DNA has been detected in normal sinonasal mucosa, albeit less frequently[5];
(ii) low levels of HPV transcriptional activity in SP[8];
(iii) both low-risk (Fig. 1) and high-risk types have been found in SPs without any consistent correlation with histological type or presence of dysplasia[5,7];
(iv) lack of consistent p16 overexpression despite the presence of high-risk HPV DNA[9]; and
(v) the very low frequency of HPV in carcinomas arising from SP.[10,11]

These observations have led some authorities to postulate that in SPs, the presence of HPV represents secondary viral colonisation of the papilloma.[5] In other words, HPV is present in as a "passenger" rather than acting as the primary aetiological agent or "driver." In SPs, since there is metaplastic change from pseudostratified ciliated columnar to a more transitional-type epithelium, it is possible that the latter is rendered more susceptible to secondary colonisation of HPV. However, evidence for this hypothesis is still lacking and further studies are necessary to determine the aetiological role of HPV in SPs. Nevertheless, despite the controversy surrounding the role of HPV in SP, most studies have found a greater prevalence of the virus in exophytic (fungiform) compared to inverted or cylindric cell (oncocytic) papillomas.[6,7]

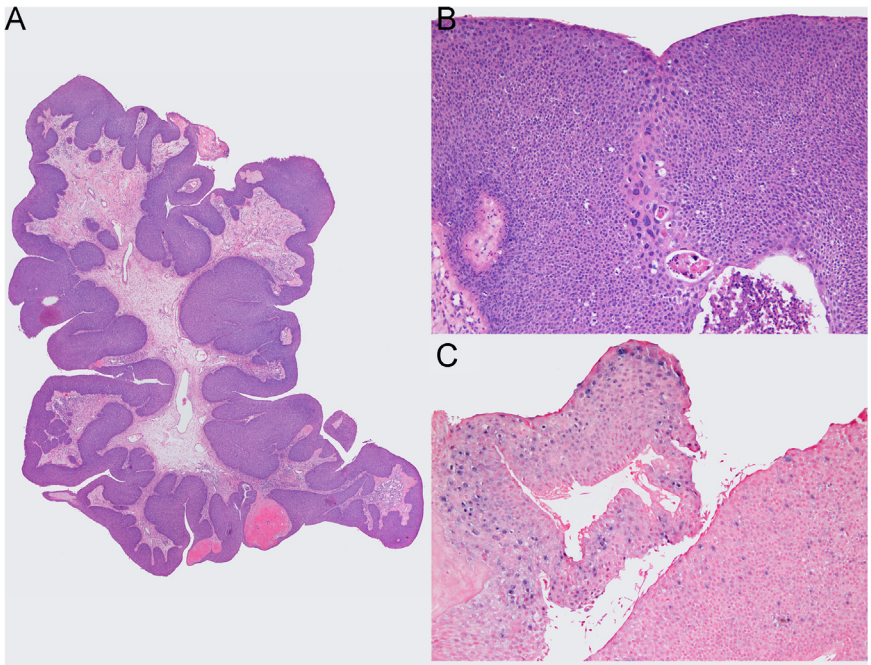

Fig. 1 – Schneiderian papilloma, inverted type. (A) Whole mount view (haematoxylin and eosin, H&E). (B) Medium power view showing cells suggestive of viral infection characterised by enlarged hyperchromatic nuclei (H&E). (C) This papilloma was focally positive for low-risk HPV DNA in situ hybridisation as demonstrated by blue staining co-localising diffusely with the epithelial cell nuclei (INFORM HPV II Family Probe 6 Probe (B), Ventana Medical Systems Inc., USA).