Histopathology of human papillomavirus-related oropharyngeal carcinoma: a review of classic and variant forms

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Abstract

Over the past decade, oropharyngeal human papillomavirus-related squamous cell carcinoma has become firmly established as a distinct entity that differs from conventional head and neck cancer in many ways including its epidemiology, genetics, tumor behaviour, and prognosis. While much attention has been given to advanced techniques for genetic profiling and viral detection in these tumors, sometimes overlooked is the fact that human papillomavirus-related oropharyngeal squamous cell carcinomas exhibit characteristic histologic features that can be appreciated by routine microscopy. In addition, there are now variant morphologies of oropharyngeal human papillomavirus-related carcinoma that are well recognized. This review will cover the classic and variant histomorphologic appearances of human papillomavirus-related oropharyngeal carcinoma, with an emphasis on their differences from conventional, human papillomavirus-unrelated cancer. Recognition of these appearances can help facilitate the performance and interpretation of human papillomavirus testing, as well as communication with treating physicians.

Keywords adenosquamous carcinoma; basaloid squamous cell carcinoma; HPV; human papillomavirus; non-keratinizing squamous cell carcinoma; small cell carcinoma

Introduction

It is now well recognized that a subset of head and neck squamous cell carcinomas is caused by high risk types of human papillomavirus (HPV).[1,2] These HPV-related squamous cell carcinomas (HPV−SCCs) differ from conventional, HPV-unrelated head and neck squamous cancers in many important ways: they have a striking predilection for the oropharynx (i.e., the palatine tonsils and base of tongue); they tend to arise in younger patients with histories of high-risk sexual practices (e.g., high number of lifetime partners, histories of oral sex) but without significant smoking histories, and, most importantly, they are associated with improved response to therapies and survival.[3−6] While the rates of conventional SCC are dropping, HPV-related oropharyngeal squamous cell carcinomas are becoming more common, to a degree that some investigators refer to this spike as an "epidemic."[7,8] The epidemiology, clinical features and oncogenic mechanisms are reviewed in greater detail by Powell and Evans in the first article of this mini-symposium.

Due to the significantly improved survival in HPV−SCCs as well as the existence of numerous clinical trials dealing with HPV−SCCs, testing for HPV has become routine for carcinomas arising in the oropharynx. Accordingly, discussions regarding which HPV detection strategy is optimal (reviewed by Moutassim et al. in this mini symposium) have taken center stage. However, sometimes overlooked in these discussions is the fact that HPV−SCCs have characteristic histologic features, and recognition of these features can help facilitate the performance and interpretation of HPV testing, as well as communication with treating physicians. After all, despite the growing list of investigatory techniques in a pathologist's armamentarium, the inexpensive, time-honoured haematoxylin and eosin-stained slide arguably remains the single most useful tool.[9]

Practice points

- HPV-related squamous cell carcinoma of the oropharynx is a distinct tumor entity in the head and neck.
- HPV-related oropharyngeal cancers tend to present in younger patients without significant smoking histories, and afflicted patients respond better to therapy and have a better prognosis when compared to HPV-unrelated cancers.
- Although HPV testing is important, the recognition of HPV-related squamous cell carcinoma begins at the light microscopic level.

Conventional (HPV-unrelated) squamous cell carcinoma morphology

Before discussing the morphology of HPV−SCC, it is worth reviewing the histologic features of conventional, HPV-unrelated SCC of the head and neck. Conventional SCC typically arises from a surface squamous epithelium that exhibits varying degrees of dysplasia and/or carcinoma in situ (Figure 1a). As the carcinoma invades through the basement membrane separating the epithelium from the sub-epithelial connective tissues, it typically induces a desmoplastic stromal reaction (Figure 1b). The invasive carcinoma invades as irregular nests and cords of epithelium that often resemble the surface epithelium, classically showing squamous differentiation in the form of squamous pearl formation (i.e., keratinization) and prominent intercellular bridges (Figure 1b). Due to abundant, keratinizing cytoplasm, conventional SCC usually has a "pink" low-power appearance. Based on how similar the tumor is in its appearance to normal squamous epithelium, the tumor is graded as well, moderately, or poorly differentiated, and this tumor grade correlates to some degree with the patient's prognosis.[10]

HPV-related squamous cell carcinoma morphology

HPV−SCC differs from conventional, HPV-unrelated SCC in many ways that are summarized in Table 1.[11] Unlike conventional SCC which can arise from the squamous epithelial lining anywhere along the upper aerodigestive tract, HPV−SCC arises

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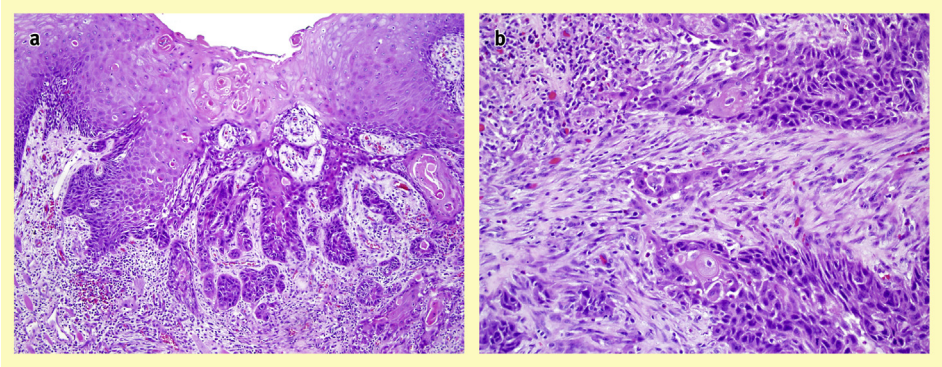

Figure 1 Conventional (i.e., HPV-unrelated) head and neck squamous cell carcinoma classically arises from a dysplastic epithelial surface (**a**), and invades as irregular nests and cords of cells with abundant keratinization while inducing a desmoplastic stromal reaction (**b**).

from the specialized lymphoepithelium of the tonsillar crypts — a fact that largely explains the anatomic site-specificity of this tumor (Figure 2). The reticulated tonsillar crypt epithelium is thought to be particularly vulnerable to HPV infection for reasons that are not entirely clear (perhaps due to its status as an immune privileged site; see review by Powell in this issue).[12] Also unlike conventional SCC, there is no recognized form of pre-neoplastic/dysplastic/in situ HPV SCC. The tonsillar crypt epithelium has a discontinuous basement membrane that does not seem to serve as a barrier to HPV—SCC, and even very small tumors that appear to be confined to a crypt are often found to have bulky lymph node metastasis.[12] When surface epithelial involvement is seen, it is thought to be the result of secondary colonization by the underlying HPV—SCC; this involvement is very abrupt unlike the typical gradual dysplastic changes associated with conventional SCC (Figure 3). As a result, all HPV—SCCs should be regarded as invasive and capable of metastasis.

HPV—SCC invades as variably-sized, smooth-edged nests and sheets of cells, and it does not classically elicit a desmoplastic reaction. Instead, HPV—SCC is typically associated with a dense tumor-associated lymphoplasmacytic infiltrate (Figure 4). At times, the lymphocytes also infiltrate the tumor itself, separating it into cords and individual cells (Figure 5). The HPV—SCC tumor cells are highly reminiscent of the tonsillar crypt epithelial cells, with indistinct cell borders, round to oval nuclei with inconspicuous nucleoli, and a high nuclear-cytoplasmic ratio with scant cytoplasm (Figure 5). HPV—SCCs have frequent tumor necrosis that can become cystic, and high mitotic rates. Keratinization and intercellular bridges — the prototypical hallmarks of conventional SCC — are typically absent or, at most, focal (Figure 6a). When keratinization is observed, it is often seen on the outside of tumor nests is a pattern that has been referred to as "reverse maturation" (Figure 6b).[13] Due to the limited cytoplasm and keratinization, the overall appearance of HPV SCC is usually "blue" in color at low power, and is often described as "basaloid" (though for reasons explained below, it is probably best to avoid this terminology in most cases of HPV—SCC). Nevertheless, despite the close correlation between histomorphology and HPV status, current guidelines recommend HPV testing of all squamous cell carcinomas arising from oropharyngeal mucosa.

When HPV—SCC metastasizes to distant sites, it unsurprisingly bears a strong resemblance to its corresponding primary

Features	Conventional SCC	HPV-related oropharyngeal SCC
Epithelial origin	Surface epithelium	Reticulated epithelium lining the tonsillar crypts
Dysplasia of surface epithelium	present	absent
Architecture	irregular cords and nests	expanding lobules
Desmoplastic stromal reaction	prominent	typically absent
Keratinization	prominent	minimal or absent
Differentiation	Ranging from well to poorly differentiated	not applicable but often interpreted as poorly differentiated

Modified from.[11]

Table 1

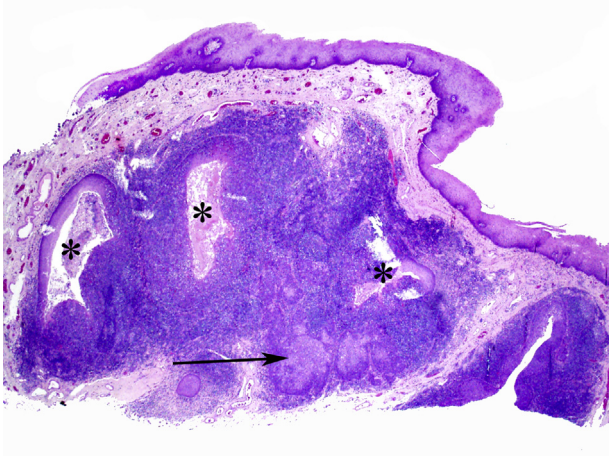

Figure 2 HPV-related squamous cell carcinoma (arrow) arises from the crypts (asterisks) of the palatine tonsil or base of tongue.