Non-squamous variants of human papillomavirus-related head and neck carcinoma

Justin A Bishop

Abstract

Human papillomavirus (HPV) is now well established as an important causative agent in a subset of head and neck cancers. HPV-related head and neck carcinomas are important to recognize because these malignancies are associated with better survival and an improved response to therapy when compared to their HPV-negative counterparts. HPV-related head and neck cancer characteristically takes the form of a non-keratinizing squamous cell carcinoma. Widespread HPV testing of head and neck tumours, however, has revealed variants that depart from the standard HPV-related squamous cell carcinoma morphology. Most recently, examples of HPV-related carcinomas that actually lack a squamous phenotype, at least partially, have been reported. This manuscript will discuss these non-squamous variants of HPV-related head and neck carcinomas: adenosquamous carcinoma, adenocarcinoma, small cell carcinoma, sarcomatoid carcinoma, and sinonasal carcinoma with adenoid cystic-like features.

Keywords adenocarcinoma; adenosquamous carcinoma; HPV; human papillomavirus; sarcomatoid carcinoma; sinonasal carcinoma with adenoid cystic-like features; small cell carcinoma

Introduction

High-risk types of human papillomavirus (HPV) are now well established as causative agents in an increasingly large subset of head and neck cancer.[1,2] These HPV-related head and neck carcinomas arise predominantly from the oropharynx, where up to 80% of carcinomas are now HPV-related.[3,4] Recently, the sinonasal tract has emerged as a second anatomic "hot spot" for HPV-related cancers.[5,6] Head and neck carcinomas arising outside of these two locations, on the other hand, only rarely harbour transcriptionally active HPV. HPV-related head and neck squamous cancers are important to recognize, because the presence of HPV is strongly associated with an improved response to therapy and better clinical outcomes.[7,8]

HPV-related head and neck cancers have a characteristic histologic appearance (Figure 1). They are typically squamous cell carcinomas that invade as sheets and lobules, frequently with zones of central necrosis. HPV-related squamous cell carcinomas exhibit minimal keratinization and do not classically elicit a desmoplastic stromal reaction. Instead, HPV-related squamous cell carcinomas are often associated with a prominent lymphoid stroma with varying numbers of tumour infiltrating lymphocytes. The tumour cells themselves have high nuclear-to-cytoplasmic ratios, open chromatin with prominent nucleoli, and a lack of prominent intercellular bridges. Taken together, these histologic features often impart a "basaloid" appearance to the tumour.

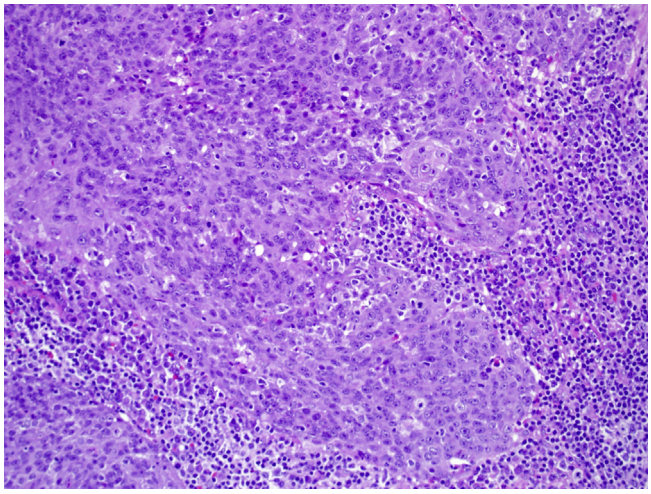

Figure 1 This carcinoma exhibits the typical morphologic features of an HPV-related oropharyngeal squamous cell carcinoma. The tumour grows in nests and sheets with a syncytial growth pattern, shows minimal keratinization, and has a prominent lymphoid infiltrate in the surrounding stroma.

Widespread testing of head and neck cancers for HPV, however, has revealed histologic variants of HPV-related cancers that depart from this characteristic morphology. Indeed, an increasing number of HPV-related head and neck cancers have been found to possess at least a component of the tumour that is actually not squamous cell carcinoma. This revelation is not altogether surprising when one considers the histologic diversity cancers of the uterine cervix, another anatomic site where HPV-related tumours predominate.[9]

Discussion

Adenosquamous carcinoma

Adenosquamous carcinoma is an uncommon biphasic tumour that consists of a component of squamous cell carcinoma in addition to a component of adenocarcinoma.[10] In the head and neck, adenosquamous carcinoma occurs most commonly in the larynx, and it has historically been regarded as an aggressive form of head and neck cancer, with frequent recurrences and locoregional metastases.[10,11] Recent examples of adenosquamous carcinoma arising from the oropharynx and the sinonasal tract have been found to be HPV-related.[5,12]

Histologically, HPV-related adenosquamous carcinoma exhibits a prominent non-keratinizing squamous cell carcinoma component, essentially identical to what is typically encountered in HPV-related squamous cell carcinoma. In addition, adenosquamous carcinoma exhibits clear-cut glandular differentiation in the form of punched-out ducts or papillary structures lined by cuboidal to pseudostratified columnar cells, or overt mucin production. Both components are high grade, with nuclear atypia, a high mitotic rate, and necrosis. The presence of mucin is

Justin A Bishop *MD Departments of Pathology and Otolaryngology/Head and Neck Surgery, The Johns Hopkins Medical Institutions, Baltimore, MD, USA. Conflicts of interest: none.*

not required for the diagnosis, but it can often be highlighted by a mucicarmine stain and can rarely be quite prominent (Figure 2). By immunohistochemistry, both squamous and glandular components are strongly and diffusely positive for p16, but only the squamous areas will be positive for the squamous markers like p63, p40, and CK5/6. In contrast, the adenocarcinoma component can sometimes be highlighted by CK7, though this is not entirely specific as a glandular marker. Both squamous and glandular areas will demonstrate punctate nuclear signals for HPV (so far all cases have been positive for type 16) by in situ hybridization.[5,12]

The main tumours to consider in the differential diagnosis of HPV-related adenosquamous carcinoma are acantholytic squamous cell carcinoma and high-grade mucoepidermoid carcinoma. On occasion, areas of HPV-related squamous cell carcinoma can become acantholytic and pseudoglandular. In this circumstance, the pseudoglandular space is typically ragged, often with dyskeratotic or necrotic debris within the pseudoluminal spaces. Unlike adenosquamous carcinoma, these tumours are diffusely positive for squamous markers, and will lack intracellular mucin. Adenosquamous carcinoma may be distinguished from high-grade mucoepidermoid carcinoma because in the former, the squamous and glandular areas are in close proximity but typically distinct and not intermingled. If present, an area of surface squamous cell carcinoma in situ — not typically present in HPV-related oropharyngeal carcinomas but sometimes seen in sinonasal examples — excludes mucoepidermoid carcinoma. Most importantly, however, finding the tumour to be positive for HPV confirms the diagnosis of a surface-derived tumour, and in my opinion essentially excludes mucoepidermoid carcinoma (see further discussion in the "Others" section below). In contrast, molecular studies detecting *MAML2* rearrangements can be helpful as these translocations are very specific for mucoepidermoid carcinoma.[13] Finally, a metastatic adenocarcinoma from a distant site to an HPV-related squamous carcinoma (i.e., a so-called "collision tumour") may be another diagnostic consideration, but finding HPV in both squamous and glandular areas of the tumour excludes that possibility.

While HPV-related adenosquamous carcinoma is rare, limited experience seems to show that it probably lacks the highly aggressive behaviour that has historically been associated with adenosquamous carcinoma.[5,12]

Adenocarcinoma

Adenocarcinomas of the mucosal head and neck are uncommon, and they most often arise from the minor salivary glands. Recent reports have drawn attention to a form of HPV-related head and neck carcinoma that is gland-forming but has minimal or no squamous component. Interestingly, all four cases of HPV-related adenocarcinomas have arisen from the base of tongue.[14–16] The tumour is histologically identical to the glandular component seen in adenosquamous carcinoma, but without a squamous component it may be difficult to recognize as an HPV-related tumour. The differential diagnosis includes a salivary-type adenocarcinoma, but the morphology of HPV-

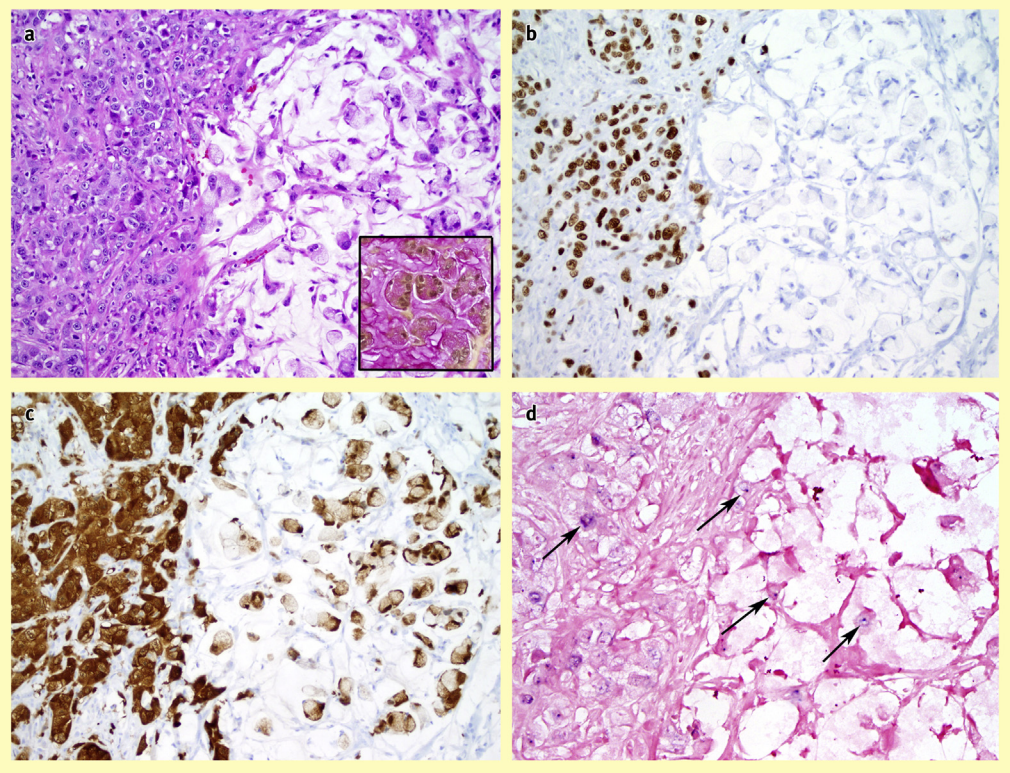

Figure 2 This HPV-related adenosquamous carcinoma has two distinct components: non-keratinizing squamous cell carcinoma on the left, and a mucinous adenocarcinoma on the right (the inset is a mucicarmine stain) (**a**). By immunohistochemistry, only the squamous component was positive for p40 (**b**). HPV testing revealed that both areas were strongly positive for p16 by immunohistochemistry (**c**) and positive for HPV DNA signals (arrows) by in situ hybridization (**d**).