CASE REVIEW

Exophytic and Papillary Squamous Cell Carcinoma of the Larynx

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Conventional squamous cell carcinoma (SCC) of the larynx presents as a largely flat or ulcerated lesion and is usually categorized histologically as *in situ*, superficially invasive, or deeply invasive. Papillary and exophytic squamous cell carcinomas of the larynx represent uncommon but distinct subtypes of SCC. As implied by their designations, these tumor types show predominant papillary or exophytic growth in the form of finger-like or filiform and broad-based bulbous fronds, respectively. Both tumor types are composed of cytologically malignant squamous epithelium. The following case illustrates the clinical and pathologic features of papillary squamous cell carcinoma and emphasizes the importance of distinguishing this entity from conventional squamous cell carcinoma of the larynx.

Squamous cell carcinoma (SCC) accounts for more than 90% of all malignant tumors of the larynx.[1] The familiar histologic features of conventional squamous cell carcinomas are divided into groups based on degree of invasion and differentiation. Factors affecting the prognosis and considered in clinical staging include tumor size, cervical lymph node metastasis, and distant metastasis.[2] Other factors of clinical importance are extracapsular spread from cervical lymph node metastases,[3] tumor location, tumor margin, and tumor differentiation or grade.[4]

A subgroup of SCC exhibiting a predominantly papillary or exophytic growth pattern has been recently described.[5] This group behaves differently from conventional SCC, and is associated with a better prognosis. In this report, we use an example of papillary SCC to define its histologic features and to compare its behavior with that of conventional SCC.

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Case Report

A 45-year-old woman had a cough with persistent hoarseness coupled with a 6-month 20-pound weight loss. She reported a 30 pack-year smoking history and acknowledged moderate alcohol use. Her hoarseness and sore throat persisted during management of symptoms. She was referred to an otolaryngologist, who identified a large, nodular and friable laryngeal mass under direct laryngoscopy, and bilateral cervical lymphadenopathy to palpation. Biopsy of the laryngeal mass revealed a moderately differentiated squamous cell carcinoma with an exophytic growth pattern. It had been diagnosed initially as a verrucous carcinoma, but this was amended after outside consultation. She then underwent a total laryngectomy and bilateral modified radical neck dissection.

Pathology

The laryngectomy specimen contained a 3.8-cm supraglottic tumor that was centered on the anterior midline, extended from the false vocal cords to 1.5 cm inferior to the tip of the epiglottis, and involved both pyriform sinuses. The mass was fungating, pink to tan, and centrally necrotic. Histologically, the tumor was predominantly exophytic with large bulbous fronds of squamous epithelium with absent to very limited keratinization; fibrovascular cores were not evident (Fig. 1). The epithelial cells had a disordered architecture, loss of polarity, cytologic pleomorphism, nuclear hyperchromasia, and increased mitotic activity, including atypical forms. The invasive component was nominal, manifested as infiltrating nests of carcinomatous epithelium. None of the 43 lymph nodes examined contained metastatic carcinoma.

Follow-up

The patient tolerated the laryngectomy well and 1 week later underwent a cricopharyngeal myotomy with tracheal–esophageal fistula formation for placement of a Blom-Singer (InHealth Technologies, Carpinteria, CA, USA)

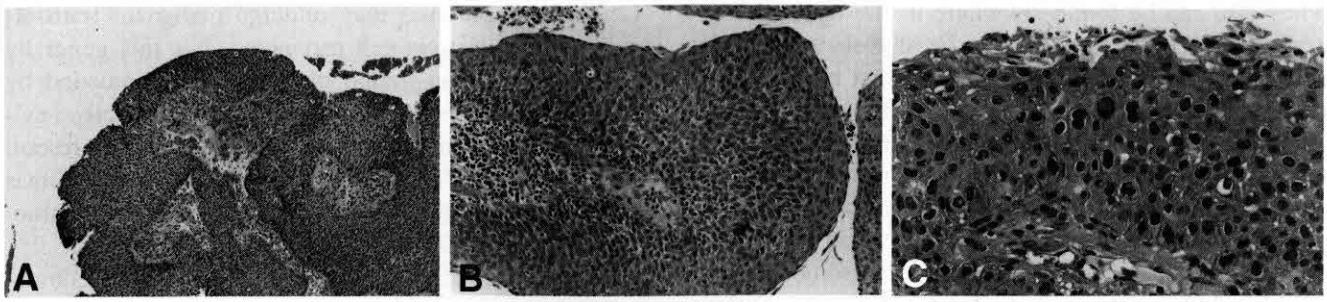

FIGURE 1. Exophytic squamous cell carcinoma of the larynx. A. The tumor projects above the plane of the laryngeal surface as bulbous, rounded fronds lined by a thickened epithelium and is generally devoid of keratinization. B. and C. At higher magnifications the malignant cytologic features of the epithelial proliferation can be appreciated.

voice prosthesis. She subsequently received a total of 6600 Gy radiation therapy. Three years later adenocarcinoma of the breast developed, and was treated with mastectomy and radiation therapy. She was alive with no evidence of recurrent or metastatic disease at last follow-up, 12 years after her laryngectomy.

Discussion

Until relatively recently, the classification of squamous cell carcinomas of the upper aerodigestive tract was all-inclusive, and the carcinomas were not distinguished on the basis of predominant growth pattern. In 1994 Ishiyama and colleagues[6] reported papillary squamous cell carcinomas of the oral cavity. These authors identified two morphologic patterns, including one with a verrucoid appearance associated with prominent keratinization, polypoid exophytic growth, and bulbous rete; and a second type that was more exophytic or papillary in appearance. From the description of the clinical and pathologic parameters of the tumors, it appears that the tumors arose in the setting of proliferative verrucous leukoplakia. In our view, Ishiyama's tumors do not represent the same group of lesions described here. More recently, Thompson *et al* [5] reported a group of laryngeal squamous cell carcinomas showing exophytic and papillary growth and attempted to distinguish these two tumors on the basis of their growth (exophytic versus papillary) and contrast their biologic behavior to conventional squamous cell carcinoma. Like conventional SCC, both exophytic and papillary SCC occur more commonly in men than in women, appear in the sixth to seventh decade of life, and are associated with tobacco and ethanol as significant risk factors. Clinical presentation includes hoarseness, changes in phonation, a husky voice, sore throat, rasping cough, or hemoptysis.

Morphologically, Thompson *et al* defined exophytic SCC as those squamous carcinomas composed of a broad-based bulbous-to-exophytic growth of squamous epithelium with multiple rounded projections that often resemble a cauliflower-like growth pattern. Fibrovascular cores can be seen but tend to be limited or absent. The papillary SCC had filiform, finger-like projections with readily identifiable fibrovascular cores (Fig. 2). In both morphologic types, the epithelial proliferation was overtly malignant. All of these tumors arose *de novo* without identification of coexisting benign lesions such as a papilloma. These tumors are often found in the larynx without predilection to any specific laryngeal site.

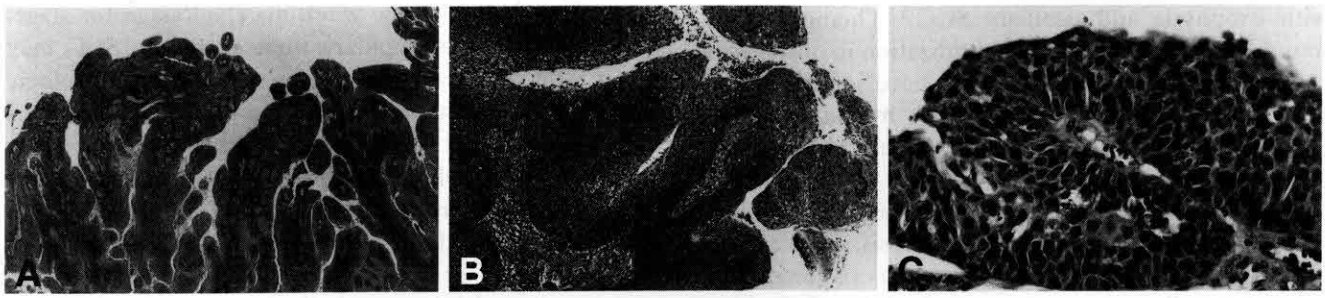

FIGURE 2. Papillary squamous cell carcinoma of the larynx. A. In contrast to the exophytic growth pattern, this tumor type shows filiform, finger-like projections with readily identifiable fibrovascular cores. B. and C. Similar to the exophytic type, the epithelial proliferation in the papillary carcinoma is overtly malignant and includes disordered architecture, loss of polarity, cytologic pleomorphism, nuclear hyperchromasia, and increased mitotic activity, including atypical forms.

They also can be found anywhere in the upper aerodigestive tract. For a tumor to be classified as either exophytic or papillary, such pattern must be the dominant growth representing more than 70% of the tumor. The squamous epithelium in both growth patterns is unequivocally malignant with nuclear hyperchromasia and pleomorphism, loss of maturation polarity, and an increase in mitotic figures including atypical forms. The overt malignant cytology identifies these tumors as carcinomas and separates them from papillomas. Surface keratinization is generally limited and often absent (nonkeratinizing), and dyskeratosis may or may not be present. The dysplastic epithelium may vary in degree of atypia but is uniformly present throughout the lesion.

Stromal invasion is usually superficial, without perineural, vascular, or cartilage invasion, and may occur as cohesive tumor nests or as individual cells. A dense chronic inflammatory infiltrate often accompanies the invasive foci. Definitive invasion may be difficult to establish in biopsy specimens, with the carcinomatous epithelium suggesting an *in situ* process rather than invasive carcinoma. However, with the formation of a clinically appreciable exophytic mass, the extent of growth goes beyond the general concept of an *in situ* carcinoma. These tumors should be considered invasive even in the absence of definitive stromal invasion. This is true even after multiple levels of the block have been performed, including reorientation of the tissue. One must consider the overall architecture in formulating a diagnosis of SCC. This may be particularly demanding when the dysplastic epithelial changes are subtle, rendering the line of distinction between SCC and atypical papilloma unclear. In these circumstances, clinical correlation and a larger biopsy may be required to appropriately diagnose and treat the patient.

Virus-associated cytopathic changes (i.e., koilocytosis) may be seen in papillary and exophytic SCC. Whereas koilocytosis is associated with human papillomavirus infection (which is an etiologic factor for laryngeal papilloma),[7] *in situ* hybridization for types 6, 11, 16, 18, 31, 33, and 51 has shown no significant correlation with exophytic and papillary SCC.[5] Thompson et al found HPV-DNA by *in situ* hybridization in only 1 of 41 cases analyzed, but other authors have identified both high- and low-risk HPV by *in situ* hybridization and polymerase chain reaction in a larger percentage of papillary SCC.[8]

The differential diagnosis of papillary and exophytic SCC includes laryngeal papillomatosis, conventional squamous cell carcinoma, and verrucous carcinoma. Laryngeal papillomas are distinguished by their bland epithelial proliferation lacking significant atypia. The latter may be focally present but does not approach the level of dysplasia seen in papillary and exophytic SCC. Certainly, papillomas may undergo malignant transformation to squamous cell carcinoma, but this generally occurs over a long period of time and is preceded by multiple recurrent papillomas. Morphologically, evidence of a coexisting (benign) papilloma may be present. In the study by Thompson et al, all of the carcinomas arose *de novo* without evidence (clinical or histopathologic) of a preexisting or coexisting papilloma.

Conventional SCC may have an exophytic component, and in a small biopsy distinction from an exophytic SCC may be impossible. In those circumstances a more general diagnosis of squamous cell carcinoma would be prudent, because treatment would be similar for both entities. We stress that the papillary or exophytic pattern must be present in greater than 70% of the tumor volume to qualify as the exophytic or papillary variant. Verrucous carcinoma is a unique tumor that is characterized by a proliferative verrucous growth pattern with marked keratosis in layers or tiers, absent nuclear atypia, absent mitotic activity beyond the basal layer, and a pushing rather than infiltrative pattern of invasion. These features contrast with those seen in papillary and exophytic SCC.

Conclusion

Papillary and exophytic SCC of the larynx represent a distinct subgroup of carcinomas with an overall better prognosis than conventional SCC, irrespective of the tumor size, location, and histologic grade. Considered *in toto* and not matched for tumor stage, papillary and exophytic SCC have absolute 5-year survival rates of 100% and 88%, respectively. The percentage of deaths from disease increases as the stage increases, but the prognosis for papillary and exophytic SCC is still better than for conventional SCC when matched for tumor stage.[5] Whereas they tend to have similar clinical courses, the papillary variant has a slightly better survival rate than the exophytic when matched stage for stage. The separation of papillary from exophytic SCC may bear little significance relative to treatment and biologic course, but it is important to recognize these tumor types as fully malignant and not to minimize them as possibly representing papillomas with cytologic atypia. Of interest, the survival rate of exophytic SCC is similar whether the tumor is glottic or nonglottic/transglottic, and whether well or moderately differentiated. Though treatment modalities are similar to conventional SCC, a more conservative approach is suggested based on the overall excellent prognosis of papillary and exophytic SCC.

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