Not Your Usual Cancer Case: Variants of Laryngeal Squamous Cell Carcinoma

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Abstract Although squamous cell carcinoma (SCC) variants account for less than 10% of all laryngeal SCCs, they have many unique biological, morphological, and clinical features. They are also easily confused with other tumor types. Recognition of them is critical for surgical pathologists as is the knowledge of what they mean for the patient. Three of the most common and important of these are basaloid, verrucous, and papillary SCC. These tumor types will be briefly reviewed with a focus on specific controversies, biological questions, and/or recent advancements in our understanding of them.

Keywords Squamous cell carcinoma · Larynx · Variants · Verrucous · Basaloid · Papillary · Human papillomavirus

Introduction

Squamous cell carcinoma (SCC) of the larynx is so common and seemingly homogeneous that one might be forgiven for assuming that they are all essentially the same. However, beyond the common keratinizing-type SCC, there are a variety of less common variants. As we progress in our knowledge and experience with them, these variants are being found to occupy unique pathologic and clinical niches. Due to their rarity, clinicians often are not knowledgeable about their clinical importance, and pathologists

may not appreciate the subtle features that define them or may not realize what entities are in the differential diagnosis. Therefore, they may not identify the tumors correctly and/or may not effectively communicate what they mean to the clinician.

SCC variants can occur anywhere along the upper aerodigestive tract (UADT), but certain types predilect for specific sites. That said, though, the larynx is the one location where almost all of them occur with regularity. SCC variants can be read about in major textbooks and in review articles so this article will not serve simply as a tutorial on them. There are, however, a number of specific controversies, biological questions, and/or recent findings related to them that are hard to find information on and which should be of great interest to the practicing pathologist and treating clinicians. This article will briefly review three of the most common, and most important, variants of laryngeal SCC, basaloid SCC, verrucous carcinoma, and papillary SCC, and will then address these specific and timely issues.

Discussion

To understand the differences in the clinical and pathologic features of the SCC variants, one has to be familiar with the typical, common type of SCC for comparison. In our practice, we term this SCC “keratinizing type” to emphasize the usually abundant cytoplasmic keratin intermediate filaments and/or extracellular keratin material that this tumor has but even more so simply to distinguish it from other histologic types of SCC. These constitute over 90% of laryngeal SCC and occur in middle to older age patients (average 60 years old), mostly male, who are almost all smokers and/or significant alcohol consumers. Spread is to local lymph nodes

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then distantly to the lungs, liver, or bone. Distant metastases occur in only approximately 10% of patients with laryngeal SCC and, from large reviews, occur across all head and neck sites in approximately 12% [1]. Survival, of course, depends greatly on stage and various clinical factors, but in general, 5 year relative survival rates are between 45 and 50% for the supraglottis, 75 and 80% for the glottis, and much lower for the subglottis [2] with an overall average of approximately 65%.

Basaloid Squamous Cell Carcinoma

Overview

Basaloid SCC, with its “blue cell” histology, is the variant most likely to be confused with other tumors. Approximately 30% occur in the larynx, the vast majority of which are supraglottic [3, 4]. It is clinically indistinguishable from other primary laryngeal SCC and has essentially the same patient demographics.

Morphology

Basaloid SCC was first described by Wain et al. in 1986 [5]. They listed four characteristic histologic features: (1) solid growths of cells in a lobular configuration, closely apposed to the surface mucosa (2) small, crowded cells with scant cytoplasm (3) dark, hyperchromatic nuclei without nucleoli and (4) small cystic spaces containing material resembling mucin. They also listed several accessory features including central “comedo-type” necrosis and stromal hyalinosis.

From practical experience, the quintessential element, and the first thing seen on low power examination, is the “jigsaw puzzle” pattern of nests of basophilic tumor cells (Fig. 1a). Just as the nuclei of a small cell carcinoma “mold” to each other, so do the nests of basaloid SCC, as if they were fashioned to fit together. The nests vary in size and can be quite large, many separated by thin lines of hyalinized, eosinophilic stroma (Fig. 1b). There commonly are rounded foci of coagulative/comedo necrosis in the center of the nests. The cells sometimes palisade at the periphery and consistently have very high nuclear to cytoplasmic ratios. The nuclei are very rounded, hyperchromatic and usually without prominent nucleoli. There is abundant mitotic activity and apoptosis. One particularly characteristic feature that is present in approximately two-thirds of basaloid SCC is stromal hyalinosis. This can take the form of thin lines between the molded nests or it can be present within the nests as pericellular hyaline material or small nodules (Fig. 1c). Evidence of keratinizing-type squamous neoplasia, whether dysplasia, invasive keratinizing-type SCC, or simply focal squamous differentiation in the basaloid tumor nests (such as keratin pearl formation) is requisite. It is usually very focal and superficial in the tumor masses (Fig. 1c).

Issue #1: Immunohistochemistry for High Molecular Weight Cytokeratins, Neuroendocrine Markers, and p63 Helps Resolve the Differential Diagnosis of Basaloid SCC with Similar Blue Cell Tumors

The H&E morphology of basaloid SCC is by far the most important feature to identify it. The differential diagnosis includes several “blue cell” tumors, three of which are the

Fig. 1 Basaloid squamous cell carcinoma. **a** Low power view showing a jigsaw puzzle-type arrangement of tumor nests ($\times 20$ magnification). **b** “Molding” of the tumor nests to one another with only thin, regular lines of hyalinized stroma between them

($\times 40$ magnification). **c** Basaloid histologic features with stromal hyalinization (*left side*) adjacent to a focus of maturing (keratinizing) squamous differentiation (*right side*) ($\times 40$ magnification)

Table 1 Differential diagnosis for “blue cell” carcinomas of the larynx

Basaloid squamous cell carcinoma
High grade neuroendocrine carcinoma (small or large cell)
Solid adenoid cystic carcinoma
Non-keratinizing squamous cell carcinoma of the oropharynx with extension to the supraglottis

most important and difficult: high grade neuroendocrine carcinoma (HGNEC), adenoid cystic carcinoma (ACC), and non-keratinizing SCC of the oropharynx [6, 7] (Table 1).

HGNEC (small cell or large cell neuroendocrine carcinoma) is seen in the supraglottic larynx as a submucosal mass of blue cells in nests and sheets. On low power, it lacks the more organized-appearing pattern of basaloid SCC. Small cell carcinoma consists of tumor cells with high nuclear to cytoplasmic ratios, and the cells are angulated and extensively molded to one another. There is a granular, stippled (“salt and pepper”) chromatin without nucleoli and frequent crush artifact. Large cell neuroendocrine carcinoma has cells with more abundant, eosinophilic cytoplasm. The nuclei are large and may have stippled chromatin but more frequently are vesicular with prominent nucleoli. Both small and large cell neuroendocrine carcinoma can have rosette-like structures. Like basaloid SCC, necrosis may be prominent and apoptosis and mitosis are frequent. HGNEC can also be mixed with squamous dysplasia or invasive keratinizing-type SCC. However, HGNEC will not have hyalinized or myxoid/mucoid stroma. The best way to tell basaloid SCC from HGNEC is by organizational and nuclear features, but immunohistochemistry is helpful. Small cell carcinoma will show dot-like staining with cytokeratins AE1/3 and CAM 5.2, and large cell neuroendocrine carcinoma will show more extensive cytoplasmic staining. Most will also be positive for the neuroendocrine markers synaptophysin, chromogranin, and CD56 while basaloid SCC, with rare exception for synaptophysin [7, 8], will be negative. Basaloid SCC is strongly positive for high molecular weight cytokeratins (34betaE12 and 5/6) while HGNEC is typically negative for these or, at most, focally positive [7, 8]. Basaloid SCC is strongly and diffusely positive for p63 while HGNEC usually shows diffuse, but weak, staining [7].

Solid-type adenoid cystic carcinoma, although rare in the larynx, enters the differential diagnosis as well. Like basaloid SCC, it characteristically has a “jigsaw puzzle” pattern of growth of basaloid cells with scattered tubular and/or cribriform structures with bluish basement membrane material. It lacks squamous differentiation and lacks extensive stromal hyalinization. Immunohistochemistry

overlaps greatly with basaloid SCC. However, one immunostain, in particular, that has been found useful to tell these tumors apart is p63, which will show patchy staining of adenoid cystic carcinoma with basal (myoepithelial) staining at the periphery of the solid nests. Basaloid SCC cells stain diffusely throughout [7].

Non-keratinizing SCC of the oropharynx, as stated, arises in the oropharynx and not the larynx. However, tumors can be large and push towards the supraglottic larynx mimicking a laryngeal primary. This is a subtype of head and neck SCC that is increasingly recognized as distinct. Virtually 100% are p16 positive, and the overwhelming majority have detectable HPV. In our experience, it is morphologically distinct from basaloid SCC, but the term basaloid SCC has been utilized variably in the literature for purely defined tumors according to Wain’s criteria and also for a portion or all basaloid-appearing SCC including non-keratinizing SCC. Like basaloid SCC, oropharyngeal nonkeratinizing SCC consists of submucosal nests of blue cells. However, it lacks the molding, “jigsaw” pattern of the nests, lacks the mucoid “gland-like” foci and the stromal hyalinization, and the nests just appear a lot more haphazardly arranged than in basaloid SCC. The nuclei of non-keratinizing SCC are much more variable and are frequently ovoid or spindled (basaloid SCC nuclei are almost uniformly round or polygonal) [4]. Both basaloid SCC and oropharyngeal non-keratinizing SCC express typical squamous antigens, so most immunohistochemistry doesn’t aid in their distinction. However, as discussed below, laryngeal basaloid SCC is almost always HPV in situ hybridization (ISH) negative and p16 negative (or weak) while oropharyngeal non-keratinizing SCC is virtually always positive. These two tests are important to utilize for this differential diagnosis and may actually supercede the differences in morphologic classification.

Issue #2: Non-Oropharyngeal Basaloid SCC is not an HPV-Driven Tumor

Given its morphology, basaloid SCC would seem very likely to be an HPV-related tumor. Although older studies demonstrated HPV by PCR in most head and neck basaloid SCC including different subsites, two more recent studies have greatly clarified this issue [3, 4] by resolving them into different prognostic entities based on anatomic subsite, p16 immunohistochemistry, and HPV ISH. In these studies, 25 (75.8%) of the 33 cases of oropharyngeal basaloid SCC had detectable HPV by ISH compared to only two (4.2%) of the 48 non-oropharyngeal basaloid SCC cases. None of the laryngeal cases had detectable HPV. All of the HPV positive cases had strong p16 expression, and outcomes diverged greatly by HPV status.

Issue #3: Laryngeal Basaloid SCC is an Aggressive Tumor with Frequent Distant Metastasis

There is some contradiction in the literature about the behavior of basaloid SCC relative to typical SCC, but as the totality is examined, it is clear that non-HPV-related basaloid SCC is more aggressive. There have been three large case control studies. Winzenburg et al. and Soriano et al. [9] showed much more aggressive behavior of basaloid SCC than for case-matched keratinizing-type SCC and more frequent nodal and distant metastases. As many as 70% of patients present with cervical lymph node metastases [9] compared with 40–50% for keratinizing-type SCC. And although reported distant metastatic rates in studies have ranged from 10 to 75%, averaging several of the largest ones shows it to occur in 35 to 40%, which is again much higher than for keratinizing-type SCC [10]. Other studies have not case matched but have found a poor prognosis for basaloid SCC relative to published rates for standard SCC [3, 4] as well.

These studies have included all different head and neck sites. Interestingly, newer studies have found that the majority of oropharyngeal basaloid SCC are HPV-related, and that they have a particularly good prognosis, akin to any other HPV-positive oropharyngeal SCC [3, 4]. The relative enrichment or lack thereof for oropharyngeal basaloid SCC cases in the studies may explain the conflicting findings across studies. For example, the one case-matched basaloid SCC study which did not show a worse prognosis consisted of 85% oropharyngeal SCC cases (which were not tested for HPV) [11]. For laryngeal basaloid SCC, the two major studies looking for HPV did not find it in cases from this site [3, 4].

The literature supports the notion that laryngeal basaloid SCC is an aggressive tumor which should signal the clinicians to do a very thorough distant metastatic workup [9] and to treat the patient aggressively.

Verrucous Carcinoma

Overview

A variant of SCC with a rich and colorful history, verrucous carcinoma (VC) was described by Dr. Lauren V. Ackerman when he was at Ellis Fischel Cancer Center in Columbia, Missouri. In this classic work in the journal *Surgery* in 1948, he outlined 31 cases of a unique type of head and neck SCC [12]. The story goes that Ackerman had diagnosed several biopsies on a patient as “papilloma”, and one day the surgeon called him to the clinic to show him a patient with a huge tumor eroding through the cheek skin. “Now what do you think of that papilloma,

doctor?” the surgeon asked. Ackerman responded “well doctor, it still looks like a papilloma, but I must say it is the BAD kind of papilloma!” He then went on to describe this unique entity.

VC is a lesion that occurs primarily in the oral cavity. However, the larynx is second most common, with virtually all cases from the glottis [13]. It is a tumor that is strongly associated with smoking, is much more common in men, and occurs at slightly older ages than typical SCC [14].

Morphology

Clinically, VC presents as a broad-based, shaggy, white, granular, non-ulcerated mass (Fig. 2). The histologic features are quite consistent, and one should be very strict in applying them to each case. Since VC consists, technically, of tumor cells that have not invaded through the basement membrane, the mass-forming and invasive nature of the lesion derives from piling up of ribbons of thick surface epithelium (Fig. 3a). The epithelium is extremely thick and cells have abundant eosinophilic cytoplasm giving them a “glassy” appearance. There is almost invariably abundant hyperkeratosis. The individual tumor cells do not show much variability. The nuclei are round to oval and, although bland, still have vesicular chromatin and prominent single nucleoli (Fig. 3b). Mitotic activity is minimal and is limited to the immediately suprabasal epithelium. These thick ribbons of epithelium, as they push together, then push outward and downward, elegantly likened to “elephant’s feet”. There is a smooth interface with the stroma, which characteristically has a florid chronic inflammatory infiltrate rich in plasma cells (Fig. 3c). The

Fig. 2 Verrucous carcinoma. Endoscopic clinical photograph of a verrucous carcinoma of the glottis (photo used with permission from Bruce H. Haughey MBChB, Washington University in St. Louis)

Fig. 3 Verrucous carcinoma. **a** Low power view showing the thick, irregular epithelium which is piling up on itself ($\times 20$ magnification). **b** Nuclei are large and round but regular in size, with vesicular chromatin and prominent single nucleoli. ($\times 400$ magnification).

c Smooth bordered, large nests of epithelium pushing into the stroma as “elephant’s feet” with adjacent chronic inflammation ($\times 100$ magnification)

diagnosis of VC is completely dependent on seeing the epithelium pushing downward below the level of the surrounding epithelium.

Issue #1: Biopsy Specimens from VC Require Precise Wording and Correlation with the Clinical Findings

Since the very characterization of this entity by Dr. Ackerman derived out of diagnosing the tumor microscopically but without clinical correlation, one can imagine that the biopsy diagnosis of VC is difficult. One important lesion that enters the differential diagnosis is verrucous hyperplasia. Verrucous hyperplasia is the identical verrucous morphology to VC but in a lesion which does not show downward pushing growth. It occurs in the oral cavity almost exclusively and is fortunately very uncommon in the larynx. When faced with a small biopsy showing the above features, one must look for the pushing invasion. If it is convincingly present, the diagnosis is VC. If not, then we prefer the term “verrucous squamous proliferation” with a comment explaining the differential diagnosis and clinical import. Particularly in the larynx, this diagnosis should be managed with serious concern by the clinician, regarding the lesion as VC until proven otherwise.

Also critical to the diagnosis of VC on biopsy is the acknowledgement that just because a biopsy shows VC, this does not assure that typical invasive keratinizing-type SCC is not also present in the lesion. This can only be ruled out on a full surgical resection specimen and occurs 10–20% of the time [15]. These tumors have metastatic potential and should be diagnosed and treated just as typical, keratinizing-type SCC. Such tumors have been termed

“hybrid” carcinoma, but we caution against the use of this term, preferring the use of “invasive (*given type of*) squamous cell carcinoma arising in verrucous carcinoma” instead.

Issue #2: VC is Strictly a Non-Dysplastic Neoplasm in which Tumor Cells have not Breached the Basement Membrane

Pure VC should not have overt cytologic atypia or, simply stated, the diagnosis is something else [12]. Dr. Ackerman reportedly used to express this fact by stating: “If the lesion looks cytologically like carcinoma, it is not verrucous carcinoma.” The differential diagnosis is presented in Table 2. What, then, does one do with a squamous neoplasm that has verrucous features yet has frankly dysplastic nuclear features or areas of infiltrative growth along its base? A variety of terms have been used for such lesions including VC with dysplasia, atypical VC, and well-differentiated SCC with verrucous features. We favor the latter term, using it for a SCC that for all the world looks like a VC but which has dysplastic nuclear features or limited, irregular interface with the underlying stroma.

Table 2 Differential diagnosis for verrucous-appearing squamous lesions of the larynx

Verrucous hyperplasia
Verrucous carcinoma
Well-differentiated squamous cell carcinoma with verrucous features
Squamous cell carcinoma arising in verrucous carcinoma

Such lesions may occupy a clinical spectrum between VC and typical invasive keratinizing-type SCC, but formal studies need to be performed to address this issue.

SCC arising in VC should show areas typical for VC but with other areas of histologically typical, frankly malignant and infiltrating SCC which is almost always of the keratinizing type. This sometimes occurs only in recurrent tumors. Such tumors are biologically essentially equivalent to typical head and neck SCC and should be managed as such, stage for stage.

Issue #3: VC Frequently Harbors HPV, but Outcomes are not Clearly Related to the Presence of the Virus

Numerous studies have evaluated VC for HPV, mostly by polymerase chain reaction (PCR). Across all head and neck subsites, approximately 35–45% of cases are positive with a wide variety of HPV types. Low risk HPV types make up as much as 65% and high risk types, particularly type 16, make up approximately 30–35% [16]. In the larynx specifically, the rate of HPV detection is similar, if not higher, with approximately 45% of cases harboring high risk HPV types, particularly 16 and 18. Interestingly, p16, the surrogate marker of HPV which signals active viral transcription, is reportedly overexpressed in most VC. This suggests a biologically-active role for the HPV [17], but no one has adequately addressed this to date. Further, no one has correlated presence or absence of HPV with risk of recurrence, transformation to frankly invasive SCC, or clinical outcomes. So, much like non-oropharyngeal SCC in general, the role of HPV in the pathophysiology and clinical behavior of VC is unknown. It likely is involved in tumor formation but does not stratify outcomes.

Papillary Squamous Cell Carcinoma

Overview

The diagnosis of papillary SCC requires the tumor to have an exophytic, papillary growth pattern, with or without frankly stromally invasive carcinoma. How much of the tumor must be papillary/exophytic has varied. The WHO says “predominantly” papillary (thus assume 50%), but some have used a cutoff of at least 70% [18]. It is most common in the larynx, primarily in the glottis [18], with the same demographics as typical laryngeal keratinizing-type SCC. Papillary SCC also occurs in the oropharynx and nasal cavity [19].

Morphology

Grossly, papillary SCC consists of delicate, frond-like projections growing as a primarily exophytic lesion projecting into the lumen. Histologically, the papillae are generally delicate with well developed fibrovascular cores and are lined by markedly dysplastic squamous epithelium with little or no maturation (Fig. 4a). The papillae are usually broad-based and somewhat fused, with multiple central fibrovascular cores, but some perfectly delicate, non-fused papillae can be seen. The tumor cells are most often non-keratinizing with high nuclear to cytoplasmic ratios and little cytoplasm (Fig. 4b) but can be more keratinizing with abundant eosinophilic cytoplasm [20, 18]. Surface keratinization is usually minimal or absent regardless of the amount of cytoplasm of the tumor cells. Frankly invasive SCC consists of nests or small collections of tumor cells invading in a stellate or irregular manner with desmoplasia or associated inflammation (Fig. 4c).

Fig. 4 Papillary squamous cell carcinoma. **a** Delicate papillary growth of the tumor ($\times 40$ magnification). **b** Non-keratinizing, full thickness dysplastic epithelium ($\times 400$ magnification). **c** Invasive

squamous cell carcinoma component showing large, irregular nests in a fibrotic stroma ($\times 100$ magnification)

Issue #1: Papillary SCC is not Equivalent to a Papilloma which has Acquired Dysplasia or Invasive Carcinoma

In the larynx, squamous papilloma with dysplasia/atypia enters the differential diagnosis for papillary SCC. However, while squamous papillomas and papillary SCC occur in the same anatomic locations, there is no clear relationship between them. Patients with upper respiratory papillomatosis are not necessarily at increased risk of any type of SCC. Among papillary SCC cases, only 13 of the 173 patients (7.5%) in three of the largest series [18, 21, 20] had a history of papilloma. In addition, as mentioned previously, papillary SCC happens in older patients, the vast majority of whom are smokers and/or drinkers. Morphologically, papillary SCC will have diffuse, marked, cytologic atypia whereas squamous papilloma with dysplasia or carcinoma will show it to be focally developing out of a background, non-dysplastic papilloma. Finally, mixed histologic patterns of benign papillomas along with the papillary SCC have only been reported in a handful of patients with papillary SCC [21, 22].

Issue #2: Papillary SCC, Even in the Larynx, is Frequently Associated with Transcriptionally-Active High Risk HPV

While the older literature has analyzed papillary SCC for HPV by different methodologies, predominantly PCR, more recent studies have utilized improved in situ hybridization (ISH) assays for high risk HPV DNA. Studies utilizing PCR have shown approximately 45% of cases to harbor HPV. The two most recent studies have shown HPV by DNA in situ hybridization in four of 14 (29%) [21] and 15 of 31 (48%) [20] cases across all head and neck sites and HPV types. For the latter study, specific data for the larynx could be discerned, and six of the 11 (54.5%) laryngeal papillary SCC were positive for p16 overexpression. Of these six, two (33%) were positive for high risk HPV by DNA in situ hybridization [20].

So as the role of HPV in oropharyngeal and sinonasal papillary SCC is apparent, it is not so clear in the larynx. However, high risk HPV is detectable in a significant number of laryngeal cases, many with evidence of active viral transcription, so this may be a significant factor in their biology.

Issue #3: The Prognosis of Papillary SCC is Favorable, and this may Correlate with the Amount of Invasive SCC Present

It is suggestive from the literature that papillary SCC of the larynx has a better prognosis than typical keratinizing-type

SCC [18], but this may depend on the criteria used for its diagnosis. In the largest series, Thompson et al. defined papillary SCC as being at least 70% papillary/exophytic. They reported 104 cases in which approximately 35% developed recurrent disease with only 10% developing nodal and/or distant metastases. Only 20% of patients died of their disease, and it was over a prolonged clinical course with an average survival of 4–5 years.

Of the 22 patients in a series by Ishiyama et al. (neoplasms they termed “exophytic papillary squamous neoplasms”), only 3 (13%) of patients had disease recurrence, 1 (4.5%) had nodal metastasis, and no patient died of disease [22]. By contrast, though, in other series by Jo et al. [20] and Suarez et al. [21] the clinical behavior has been somewhat more akin to keratinizing SCC. Importantly, these latter three series did not define the amount of papillary tumor versus invasive for making the diagnosis. Interestingly, the larynx was the subsite with the best prognosis.

The reasons for the apparently improved prognosis may be that most (and sometimes all) of the neoplasm is growing on the surface without basement membrane invasion and also that some of the tumors, even in the endolarynx, have biologically active HPV [20]. What is important is stringency in the diagnosis. Based on the literature, one must have a tumor that is at least predominantly papillary or one may choose to apply the even more strict criterion of 70% when making this diagnosis.

Conclusion

These three major variants of laryngeal SCC are unique, and awareness of their particular histologic and biologic features will assure a proper diagnosis. As knowledge about them grows and HPV and other molecular pathways and biomarkers are investigated by modern methods, we can expect them to be even more clearly defined and perhaps more uniquely treated.

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