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MINI-SYMPOSIUM: HEAD AND NECK PATHOLOGY

Squamous cell carcinoma variants of the head and neck

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squamous cell carcinoma;
sarcomatoid carcinoma;
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exophytic carcinoma;
papillary carcinoma;
verrucous squamous cell carcinoma;
adenosquamous carcinoma

Summary Variants of squamous cell carcinoma (SCC) frequently arise within the mucosa of the upper aerodigestive tract, accounting for up to 15% of SCCs in these areas. The most common variants include verrucous, exophytic or papillary, spindle-cell (sarcomatoid), basaloid and adenosquamous carcinoma. Each of these variants has a unique histomorphologic appearance, which raises a number of different differential diagnostic considerations, with the attendant clinically relevant management decision.

Verrucous squamous cell carcinoma has a broad border of pushing infiltration of a non-dysplastic squamous epithelium, essentially devoid of mitotic figures, displaying hyperkeratosis on elongated rete pegs. Papillary and exophytic SCC have a papillary or exophytic architecture, but have malignant cytologic features within the epithelium. Spindle-cell (sarcomatoid) carcinoma is an SCC blended with a spindle-cell morphology, frequently mimicking other mesenchymal tumours. Epithelial markers are often negative. Basaloid SCC is a high-grade SCC variant with small cells arranged in a palisaded architecture, with hyperchromatic nuclei and only focal areas of squamous differentiation. Adenosquamous carcinoma is a rare variant, which is a composite of adenocarcinoma and squamous cell carcinoma, often with areas of transition. The cytomorphologic features are described in detail in an attempt to allow the general surgical pathologist to separate these variants of SCC in order to achieve appropriate clinical management.

INTRODUCTION

The histologic classification of malignant tumours is not only of academic interest from a histogenetic viewpoint, but also from that of treatment and prognosis. Squamous cell carcinoma (SCC) is by far the most important and most common malignant mucosal neoplasm to affect the head and neck, accounting for over 90% of all malignant neoplasms. SCC is generally divided into three histologic categories: *in situ*, superficially invasive or deeply invasive carcinomas, with additional modifiers based on histologic grade, including well, moderately or poorly differentiated, along with the presence or absence of keratinization. SCC can be ulcerative, flat, polypoid, verrucous or exophytic. Occasionally, variants of squamous cell carcinoma will be encountered by the busy general surgical pathologist. These variants make up in aggregate about 10–15% of all SCCs, including verrucous, exophytic or papillary, spindle cell (sarcomatoid), basaloid and adenosquamous carcinoma (Table 1). This short treatise is designed to give a brief overview of the clinical features, aetiologic factors, macroscopic findings, microscopic features, immunophenotypic reactions and management alternatives available for the most common squamous cell carcinoma variants. Before discussing variants, it is perhaps wise, although axiomatic, to present a short discussion on conventional SCC.

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SQUAMOUS CELL CARCINOMA

SCC affects more men than women, usually in the middle to later decades of life, although any age can be affected. The most important risk factors are, independently, tobacco (cigarette, cigar, pipe, smokeless) and alcohol,[1–4] although susceptibility (immunologic

Table I Clinical and histologic features of squamous cell carcinoma variants

Feature	Variant				
	Verrucous	Papillary/exophytic	Spindle cell (sarcomatoid)	Basaloid	Adenosquamous
Gender	M > F, except oral	M ≫ F	M ⋙ F	M ≫ F	M slight > F
Location	Oral > larynx	Larynx > oral > nasal	Larynx > oral > nasal	Base of tongue > supraglottic larynx	Tongue > floor of mouth > nasal
Frequency (of all SCC)	3%*	1%*	3%*	< 1%	< 1%
Aetiologic agent?	HPV	? HPV	? Radiation	Unknown	Unknown
Macroscopic	Broad-based warty and fungating mass	Polypoid, exophytic, bulky, papillary, fungiform	Polypoid mass	Firm to hard with central necrosis	Indurated submucosal nodule
Size (cm)	Up to 10	1–1.5 (mean)	2 (mean)	Up to 6	1 (mean)
Microscopic	Pushing border of infiltration; abrupt transition with normal; large, blunt club-shaped rete pegs; no pleomorphism; no mitotic activity; abundant keratin, including parakeratin crypting and 'church-spire' keratosis	> 70% exophytic or papillary architecture; 'cauliflower-like' vs. 'celery-like,' unequivocal cytomorphologic malignancy; surface keratinization; invasive, but difficulty to demonstrate; koilocytic atypia	Biphasic; SCC present, but ulcerated; blended/transition with atypical spindle cell population; hypercellular; variable patterns of spindle-cell growth; pleomorphism; opacified cytoplasm; increased mitotic figures	Biphasic; invasive; lobular; basaloid component most prominent; palisaded; high N:C ratio; abrupt squamous differentiation (metaplasia, dysplasia, carcinoma *in-situ* or invasive); ↑ mitotic figures; comedonecrosis; hyaline material	Biphasic; SCC and adenocarcinoma; undifferentiated component; separate or intermixed with areas of transition; infiltrative; ↑ mitotic figures; sparse inflammatory infiltrate
Special studies	HPV identified	None	70%* positive with epithelial markers	Keratin, EMA, CK7 and 34ßE12	Mucin positive adenocarcinoma cells
Differential diagnosis	Verrucous hyperplasia; SCC	*In-situ* SCC; squamous papilloma; reactive hyperplasia	Benign and malignant mesenchymal processes; melanoma; synovial sarcoma	Adenoid cystic carcinoma; neuroendocrine carcinoma (small-cell carcinoma)	BSCC; mucoepidermoid carcinoma; adenocarcinoma with squamous metaplasia
Treatment	Surgery	Surgery ± radiation	Surgery with radiation	Surgery; radiation; chemotherapy	Surgery with neck dissection
Prognosis	75% 5-year survival	70%* 5-year survival	80%* 5-year survival	40%* 2-year survival	55%* 2-year survival
Pitfalls	Inadequate biopsy; tangential sectioning	Orientation; adequacy of specimen	No surface; mesenchymal markers; Needs 'excisional' biopsy initially	Association with 2nd primary; High chance of nodal metastases	Separation on small biopsies from adenocarcinoma or SCC

BSCC, basaloid squamous cell carcinoma; EMA, epithelial membrane antigen; HPV, human papilloma virus; SCC, squamous-cell carcinoma; *, approximate figures.

factors and age), environmental and occupational factors may also play a role. Viruses (human papilloma virus, Epstein-Barr virus) are also linked to the development of SCC,[5–7] although association versus direct effect remains unresolved. Genetic predisposition to SCC is well recognized, although it comprises only a small subset of clinical SCC.[8] Deletion, allelic imbalances or loss of heterozygosity (LOH) on the short arm of chromosome 3 has been associated with a more aggressive biologic behaviour, as well as having therapeutic implications in SCC of the head and neck.[9,10] No doubt all of these factors probably interact in a multifactorial process.

Mucosal SCC arises anywhere in the head and neck, although the tongue is most affected in the oral cavity, the maxillary sinus in the sinonasal tract and the glottis in the larynx.[11–13] SCC can be ulcerative, flat, papillary or exophytic in growth, ranging from minute mucosal thickenings to large masses filling the luminal spaces. The tumours are erythematous to white to tan, frequently feeling firm on palpation. 'Conventional' SCC is composed of variable degrees of squamous differentiation, with well-differentiated cells almost perfectly recapitulating normal squamous epithelium, but demonstrating basement membrane violation by nests of tumour cells. SCC shows disorganized growth, a loss of polarity, dyskeratosis, keratin pearls, intercellular bridges, an increased nuclear to cytoplasmic ratio, nuclear chromatin irregularities, prominent eosinophilic nucleoli and increased mitotic figures (including atypical forms). Keratinizing-type is not seen as frequently as the non-keratinizing or poorly differentiated types. Mitotic figures and necrosis tend to increase as the grade of the tumour becomes more poorly differentiated. A rich inflammatory infiltrate (usually of lymphocytes and plasma cells) is seen at the tumour to stroma junction, along with a dense, desmoplastic fibrous stroma. The poorly differentiated lesions only have a vague resemblance to squamous epithelium, with only rare foci of squamous differentiation. Perineural invasion can be seen, with a positive correlation to metastatic potential.[14] Special studies are rarely needed to document the epithelial nature of the tumour. Instead, tumour location, size, histology (poorly differentiated), degree of invasion, lymph-node metastases (especially when there is extranodal capsular extension) and multifocal disease all correlate with a poorer prognosis.[11–13,15]

The differential diagnosis is generally limited to papilloma and hyperplasia. The histologic distinction of papilloma in adults from well-differentiated SCC relies on disorganized growth and unequivocal morphologic features of malignancy. Marked pseudoepitheliomatous hyperplasia (PEH) may be mistaken as SCC. However, the reactive nature of the proliferation, lack of 'finger-like' invasion and the frequent association with infectious agents or granular cell tumour will help to make this distinction.

VERRUCOUS SQUAMOUS CELL CARCINOMA

The demographics for verrucous squamous cell carcinoma (VSCC) are identical to conventional SCC, although oral cavity VSCC is more common among older women.[16] VSCC comprises about 3% of all SCC, diagnosed in the oral cavity in an estimated one of every million persons each year.[17] A direct and active pathogenetic role has been ascribed to human papilloma virus in the development of VSCC, and specific loss of heterozygosity patterns are seen in carcinoma and not hyperplasia.[3,18] The gross appearance is usually of a broad-based, warty, exophytic or fungating, bulky, firm to hard, tan or white mass measuring up to 10 cm in greatest dimension. The papillary-exophytic structures may show surface ulceration. No specific anatomic location is exempt from this neoplasm, although the oral cavity is more commonly affected than the larynx, with the remaining cases in the sinonasal tract and nasopharynx.[16,19–24]

VSCC is a highly differentiated type of SCC (also called Ackerman's tumour), composed of an exophytic, warty tumour with multiple filiform projections, which are thickened and club-shaped, and lined by well-differentiated squamous epithelium. The advancing margins of the tumour are usually broad or bulbous rete pegs, with a pushing rather than an infiltrative appearance, and a dense inflammatory response in the subjacent tissues (Fig. 1). The epithelium is extraordinarily well differentiated without any of the normally associated malignant criteria identified in SCC. The cells are arranged in an orderly maturation towards the surface, with abundant surface keratosis (orthokeratosis; called 'church-spire' keratosis; Fig. 2). Parakeratotic crypting is a common feature. Mitotic figures are not easy to identify and, when found, are not atypical. Focal atypia/dysplasia must be limited to the basal zone if present.[16,19–24] As both a benign keratinizing hyperplasia (or verruca vulgaris) and a very well-differentiated SCC can share all of these features somewhere in the tumour, it is easy to understand that determining which biopsies are to be included within the spectrum of VSCC, or excluded from it, is a most vexing problem for the surgical pathologist. Specifically, in small or superficial biopsies, these features may be seen throughout all biopsy fragments. Therefore, verrucous lesions must only be called carcinoma when the relationship of the lesion to the stroma can be adequately assessed (often at the time of complete surgical excision).

VSCC is probably one of the most difficult and problematic lesions to diagnose in almost every instance. This is because the lesion is not cytologically malignant and therefore evidence of invasion is required for definite diagnosis. However, definite histologic evidence of invasion in the limited and small biopsies usual in the head and neck make it difficult or impossible to ascertain. With a large and mostly exophytic lesion, the biopsies, even

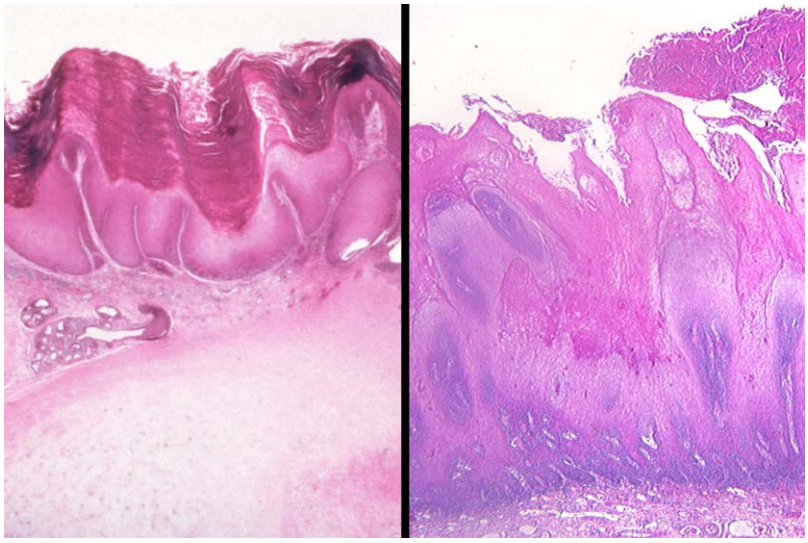

Figure 1 Verrucous squamous-cell carcinoma demonstrating a broad pushing border of infiltration with an exophytic expansion of the epithelium with keratosis (church-spire type). Left image demonstrates the underlying laryngeal cartilage.

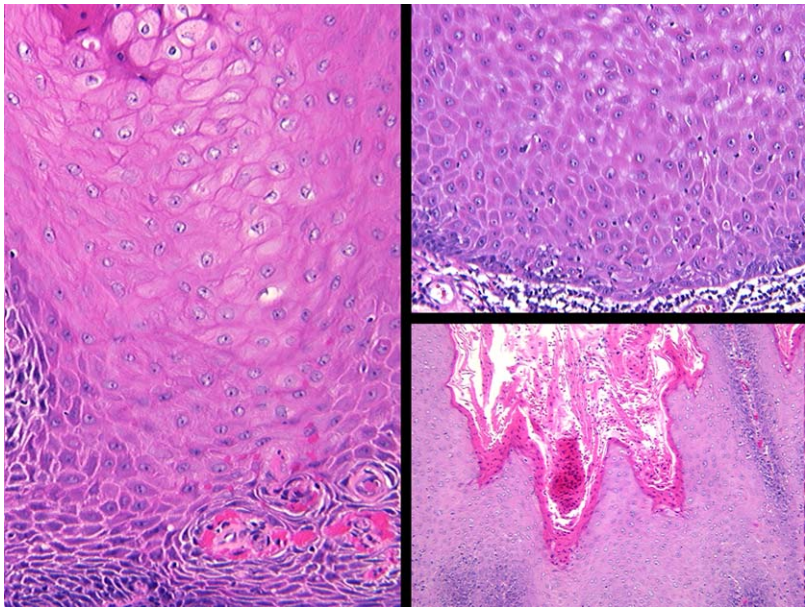

Figure 2 The proliferation is cytologically bland without mitotic figures (left), but demonstrating a broad, bulbous-type infiltration into the stroma with associated inflammation (right upper). Keratosis is noted (right lower).

when generous in volume of tissue, will usually not include much if any of the stromal interface at the lower portion of the lesion. Compounding this difficulty is the almost unavoidable tangential sectioning artifact of the curled, piecemeal or fragmented biopsy (emphasized further if frozen section was requested). Attempts to judge whether or not there is invasion of broad sheets of squamous epithelium are almost routinely frustrating. This problem is not as bad in the oral cavity where it is more feasible to have a large, intact, well-orientated biopsy that demonstrates the architecture of the lower portion of the lesion.

The differential diagnosis rests between verrucous hyperplasia and conventional SCC. It has been argued that the difference between verrucous hyperplasia and VSCC is only in stage and size, the lesions representing a developmental spectrum.[24–26] The distinction on histologic features alone, even when specialized studies have been performed (including DNA analysis), is often not possible.[7,22,27,28] However, even though isolated, true verrucous hyperplasia does exist (hyperplastic squamous epithelium with regularly spaced, verrucous projections and hyperkeratosis, sharply defined at the epithelial to stromal interface), conservative management with close

patient follow-up is recommended.[26,29] If the lesion recurs, additional surgery at the time of the recurrence will avoid the untoward consequences of an early hemi- or total laryngectomy. Verruca vulgaris has a prominent keratohyaline granular layer and parakeratois, with sharply defined acanthotic rete ridges, features not seen in VSCC. Proliferative verrucous leukoplakia is characterized by multiple, persistent keratotic plaques, which will, over time, go on to develop verrucous carcinoma, although the arc of development is not always present.[29] VSCC can include an invasive component of 'ordinary' SCC at the base or demonstrate atypical cytologic features; these tumours need to be managed as well-differentiated SCC, with the attendant surgery, radiation therapy, or both. This area of separation requires the judgments of both pathologist and clinician, with communication between the two of paramount importance. The onus rests with the pathologist to be as thorough as possible in trying to ensure that the clinician understands completely what is present on the biopsy slides.

The biologic behaviour of VSCC is between non-neoplastic hyperplasia and conventional SCC,[20] but the continuum of disease does not co-operate with attempts at categorization. Therefore, it may be helpful to think of VSCC as an 'extremely well-differentiated squamous cell carcinoma' rather than a separate entity, as used in the title of this section, to emphasize the relationship of this tumour to conventional SCC. An approximate 75% 5-year relative survival is described for head and neck VSCC, although this varies depending on site and stage.[16]

From a clinical standpoint, there are two incorrect beliefs regarding VSCC. Many believe that VSCC does not metastasize and that radiotherapy is contraindicated. However, many well-differentiated SCC, even those with considerable cytologic atypia, have not metastasized at the time of initial treatment, [30–33] so it is not difficult to extrapolate that VSCC, an extremely well-differentiated SCC, at the same anatomic location would have a low metastatic rate. Considering the superficial, non-destructive invasion, and the probability that many lesions reported as verrucous carcinomas may be verrucous hyperplasia, there is a slight metastatic capacity in the group as a whole. This does not exclude the possibility of metastasis, especially if the lesion is left for long enough and allowed to become more 'invasive.'

Likewise, as conventional SCC can recur with a more poorly differentiated transformation after radiation therapy, the risk of transformation in a VSCC to a more poorly differentiated tumour has probably been overemphasized. Any well-differentiated SCC (including VSCC) generally does not respond significantly to radiation therapy. However, in patients who are not good surgical candidates, radiation therapy of a lesion diagnosed as VSCC should be considered.[16,31,33]

EXOPHYTIC AND PAPILLARY SQUAMOUS CELL CARCINOMAS

Exophytic (ESCC) and papillary squamous cell carcinoma (PSCC) are uncommon but distinct variants of SCC of the upper aerodigestive tract mucosa, separable from verrucous SCC (as outline above). By definition, ESCC and PSCC are de novo malignancies without a pre- or co-existing benign lesion (i.e. squamous papilloma). There are no specific or unique clinical or demographic parameters for this variant of SCC. The average size of exophytic and papillary tumours is about 1.5 and 1 cm in greatest dimension, respectively. Most tumours present at a low tumour stage (T1 or T2), although multifocality is described. This tumour type occurs more frequently in the larynx, followed by the oro- and hypopharynx. Macroscopically, ESCC and PSCC are polypoid, exophytic, bulky, papillary or fungiform tumours, soft to firm, arising from a broad base or from a narrow pedicle/stalk.[34–38]

By definition, the neoplastic squamous epithelial proliferation must demonstrate a dominant ($>70\%$) exophytic or papillary architectural growth pattern with unequivocal cytomorphologic evidence of malignancy. Two specific histologic growth patterns can be separated from conventional SCC. The exophytic pattern consists of a broad based, bulbous to exophytic growth of the squamous epithelium. The projections are rounded and 'cauliflower-like' in growth. Tangential sectioning yields a number of central fibrovascular cores, but the superficial aspect is lobular, not papillary. The papillary pattern consists of multiple, thin, delicate filiform, finger-like papillary projections. The papillae contain a delicate fibrovascular core surrounded by the neoplastic epithelium (Fig. 3). Tangential sectioning yields a number of central fibrovascular cores, appearing more like a bunch of celery cut across the stalk. It is not uncommon to have extensive overlap between these patterns, and when this is the case, the ESCC is the default. Both types demonstrate features of SCC, with surface keratinization (generally limited and focal), dyskeratosis, architectural disruption and distortion with loss of cellular polarity, nuclear enlargement, an increased nuclear to cytoplasmic ratio, prominent nucleoli and numerous mitotic figures. Stromal invasion can be found (cohesive or single-cell infiltration), but may require multiple sections and re-orientation of the biopsy to demonstrate definitive invasion. An associated rich chronic inflammatory response is frequently present. The invasion is usually superficial, without perineural, vascular or osseous invasion. So-called 'koilocytic atypia' is frequently focally noted, defined by hyperchromatic, crenated nuclei surrounded by a clear halo of cytoplasm and an accentuated cell border (Fig. 3). Human papilloma virus genome incorporation into the nucleus can be identified by in-situ hybridization techniques.

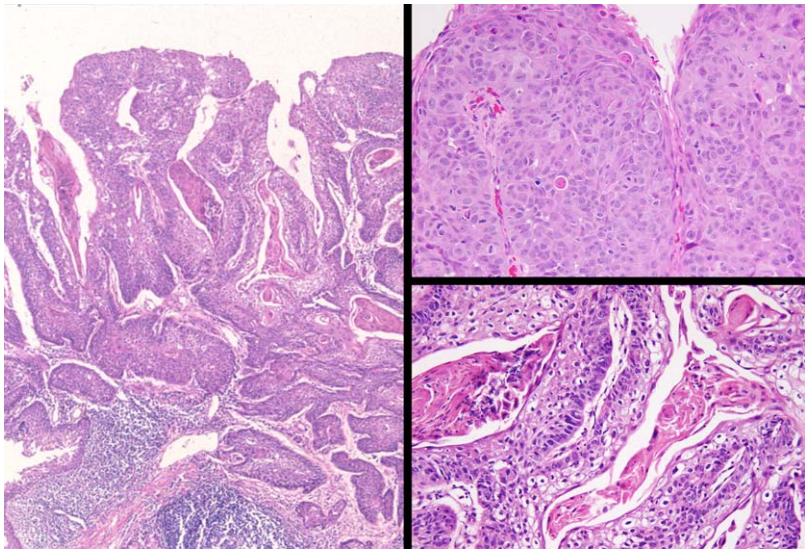

Figure 3 A papillary SCC with individual, delicate finger-like projections with fibrovascular cores (left). Cytologically atypical epithelium is identified lining the papillary projections (right upper); 'koilocytic atypia' and keratosis is frequently noted (right lower).

In a few biopsies it may be very difficult definitively to discern invasion, and the carcinomatous epithelium mostly suggests an in-situ carcinoma. However, the significant proliferation of this carcinomatous epithelium, often forming an appreciable clinical lesion, is rather beyond the general concept of carcinoma in-situ. When it is difficult to be completely confident of frank histologic invasion, the significantly proliferated appearance of the lesion should be heavily weighted in the direction of carcinoma. The cytomorphologic features of malignancy would exclude the diagnosis of a papilloma, as well as the consideration of a verrucous carcinoma. Squamous papilloma may have focal atypia, but not to the degree identified in carcinoma. Reactive inflammatory hyperplasia may have focal atypia, but generally does not have the well-developed exophytic or papillary architecture of ESCC or PSCC. Similarly, verrucous hyperplasia lacks the cytologic features of malignancy.

About one-third of patients with either pattern develop recurrence, frequently more than once. The recurrences look remarkably similar in histomorphologic appearance to the primary tumours, although there are exceptions. Recurrences can be treated with conservative measures, although occasionally laryngectomy may be needed for recalcitrant cases. Metastases, when they develop, involve the regional lymph nodes first, followed occasionally by lung, liver and bone disease. The distinction of exophytic and papillary variant of SCC is important because these patients seem to have a better prognosis when compared with location and stage-matched conventional SCC patients.[34,35] Therapeutic intervention may be modified on the basis of the overall excellent prognosis of patients with exophytic or papillary growth-pattern squamous cell carcinoma.

SPINDLE-CELL (SARCOMATOID) CARCINOMA (SCSC)

Over the years, many terms have been applied to this confounding neoplasm (carcinosarcoma, pseudosarcoma, squamous cell carcinoma with pseudosarcoma, Lane tumour), but spindle-cell (sarcomatoid) carcinoma (SCSC) is recognized as a morphologically biphasic tumour with a carcinoma that has surface epithelial changes (dysplasia to invasive carcinoma) and an underlying spindle-shaped neoplastic proliferation.

SCSC is an uncommon type of squamous cell carcinoma, comprising up to 3% of SCC. There is a profound male to female ratio (11 : 1) and generally the tumour occurs in individuals in their seventh decade of life, although patients can present within a wide age spectrum.[39–45] Symptoms are often present for a short duration, especially when considering the anatomic confines of the larynx. Radiation exposure may be an aetiologic agent in a few cases. Nearly all cases are described or received as polypoid masses (especially if they are laryngeal), with a mean size of about 2.0 cm. They are frequently ulcerated with a covering of fibrinoid necrosis. They have a firm and fibrous cut surface. Similar to conventional SCC, most tumours are T1 lesions at presentation.

Considering the frequency of surface ulceration with fibrinoid necrosis, it may be difficult to discern the transition between the surface epithelium and the spindle cell element. If meticulously and diligently sought, dysplasia, carcinoma *in-situ*, or infiltrating SCC, can be identified, although it is usually minor to inconspicuous, with the sarcomatoid part dominating (Fig. 4). Areas of squamous differentiation are most consistently identified at the base of the polypoid lesion, at the advancing margins, or

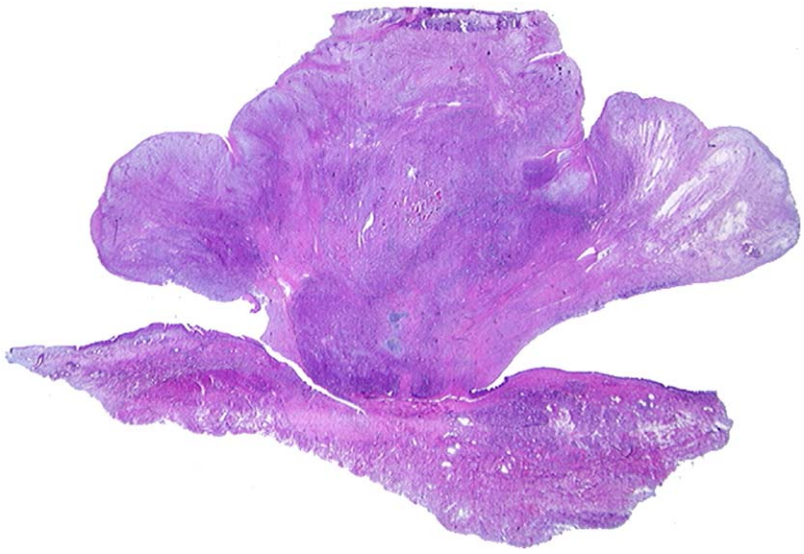

Figure 4 Polypoid projection attached to the underlying stroma of the larynx by a narrow stalk or pedicle. No invasion into the laryngeal soft tissues is seen. Surface ulceration has denuded most of the epithelium.

within invaginations at the surface where the epithelium is not ulcerated or denuded. SCSC will often present with little invasion into the underlying stroma, as it is polypoid.

The carcinomatous and sarcomatoid components will abut directly against one another, with areas of barely perceptible blending and continuity between them (Figs 4 and 5). At times, the area of elongation and spindling seems to arise from the basal epithelial cells, making indistinct any demarcation between the surface epithelial origin and the underlying tumour. The sarcomatoid or fusiform fraction of the tumours can be arranged in a diverse array of appearance, imitating a number of different mesenchymal processes (Fig. 5): storiform, cartwheel, or whorled: resembling a fibrous histiocytoma or malignant fibrous histiocytoma; intersecting and interlacing bundles or fascicles: similar to leiomyosarcoma or malignant peripheral nerve sheath tumour; chevron or herringbone: indistinguishable from fibrosarcoma; hypocellular with dense collagen: comparable to fibromatosis; loose, random grouping with a degenerated background: analogous to nodular fasciitis. Tumours are generally hypercellular, although hypocellular tumours are recognized. There is no maturation phenomenon. Pleomorphism is often mild to moderate, without a severe degree of anaplasia. The tumour cells are plump fusiform cells, although they can be rounded and epithelioid. Opacified, dense, eosinophilic cytoplasm, give a hint of squamous differentiation, but is difficult to quantify or qualify accurately. Giant cells of a variably type can be seen dispersed throughout the neoplasm. Mitotic figures, including atypical forms, are easily counted in most tumours, whereas true tumour necrosis is rare. As would be expected with an infiltrative neoplasm, chronic inflammatory cells can be seen at the base. Rarely, metaplastic or frankly neoplastic cartilage or bone can be seen.

SCSC is the one SCC variant in which the application of immunohistochemistry may be of value. If the surface epithelium is present, it serves as a good internal control, but it is frequently lost. The individual spindle neoplastic cells react variably, although most sensitively and reliably with keratin (AE1/AE3), epithelial membrane antigen and CK18. Unfortunately, only about 70% of cases will yield any epithelial immunoreactivity. A number of other mesenchymal markers can be identified focally, including smooth muscle actin, muscle-specific actin, and rarely, S-100 protein.[40,41,45,46] This phenotypic plasticity is expressed by a loss of intercellular cohesion, elongation of the cells, loss of basement membrane, production of connective tissue (collagen) and invasion into the stroma. This type of lineage infidelity is to be expected in a tumour that has demonstrated sarcomatoid transformation to the degree seen in SCSC. Whereas a positive epithelial marker can help to declare the diagnosis of SCSC, a non-reactive or negative result should not dissuade the pathologist from the diagnosis, especially in the larynx.

The differential diagnosis for any spindle cell tumour is most challenging. It includes a number of benign and malignant processes, such as fibromatosis, leiomyoma, nodular fasciitis, fibrosarcoma, malignant fibrous histiocytoma, leiomyosarcoma, rhabdomyosarcoma, malignant peripheral nerve sheath tumour, mesenchymal chondrosarcoma, Kaposi's sarcoma, angiosarcoma, synovial sarcoma, and malignant melanoma, to name just a few. It is easy to see how the magnitude of diagnostic differentials can be a source of frustration for the pathologist. An exhaustive review of each of these lesions in this monograph is precluded by spatial constraints, but

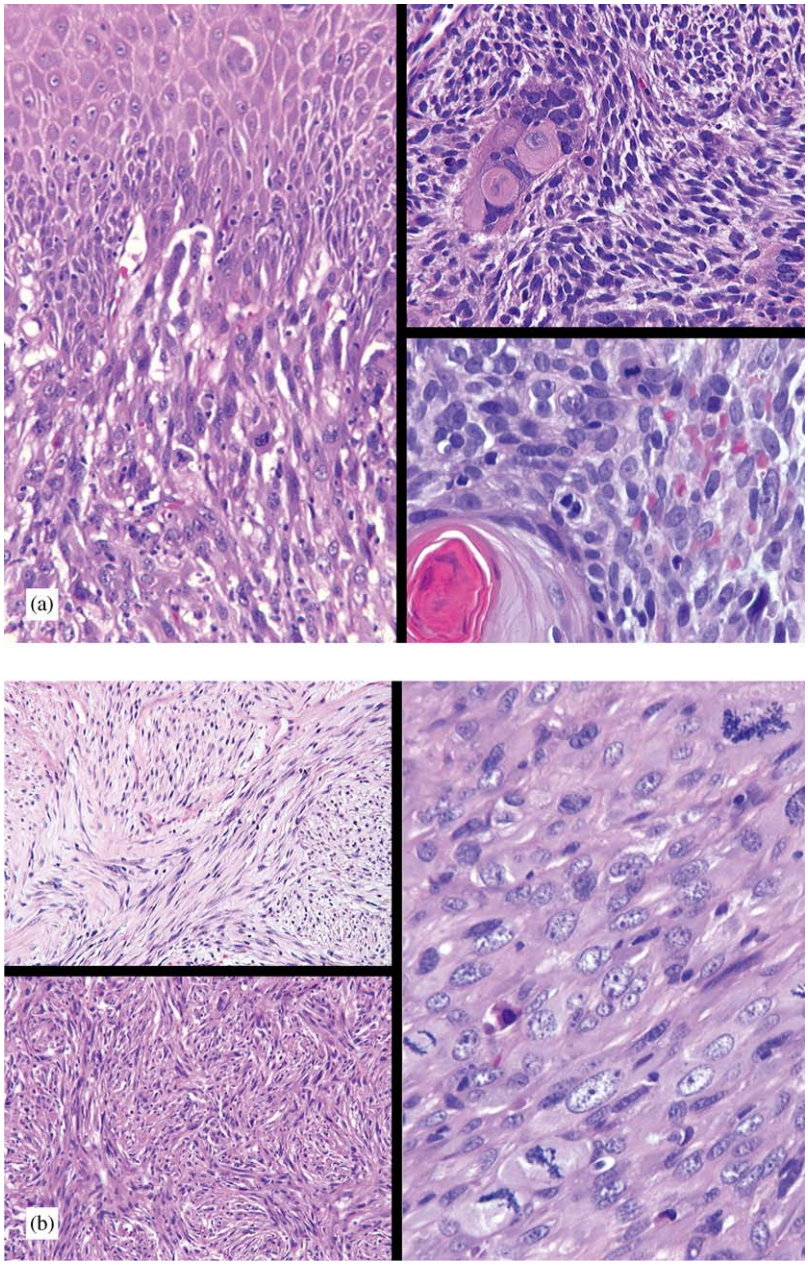

Figure 5 A. A blending of the surface epithelium with the spindle-cell component in a spindle cell (sarcomatoid) carcinoma (left). Abrupt transitions with conventional squamous cell carcinoma can be seen (right, upper and lower). B. Variable patterns of growth are seen in a spindle cell (sarcomatoid) carcinoma, including fascicular and storiform (left), composed of atypical spindle cells with increased mitotic figures, including atypical forms (right).

suffice it to say that authentic primary mucosal sarcomas or benign mesenchymal tumours are rare. Whereas sinonasal tract and oral cavity mesenchymal and neural/neuroectodermal neoplasms occur, these lesions in the larynx are vanishingly rare. Given the polypoid nature of the tumour, and the presence of squamous differentiation in many cases, an accurate discrimination between these tumours is usually possible. Synovial sarcoma (especially monophasic) may cause the most diagnostic difficulty, but the age at presentation (children), tumour location (usually soft tissue rather than mucosal) and the presence of a specific chromosomal translocation t(X; 18)(p11; q11) can aid in this distinction. Also included in the differential diagnosis is the mere recognition that the tumour is malignant. This is often not too difficult as most spindle cell carcinomas are moderately densely cellular tumours with many cells having significant malignant characteristics. However, some tumours develop a dense stromal connective tissue and are hypocellular. The cells in these tumours may be difficult or impossible

to recognize as cytologically malignant. In this event, the distinction from a benign myofibroblastic inflammatory pseudotumour relies on the latter's tendency to be circumscribed, to have cells with 'feathery' cytoplasmic appearance, and a lack keratin immunoreactivity.

Surgery, usually followed by radiation therapy, seems to yield the best long-term patient outcome, similar to conventional squamous cell carcinoma. All authors agree that tumour location (tongue, pharynx, glottis) and tumour stage (TI, T2, T3 and T4) are the two most important factors influencing the management and outcome of patients with SCSC.[39–45] It is imperative to reiterate that all patients have a diagnostic biopsy before the definitive therapy, which may 'cure' the patients. This is predicated on the concept that the tumours are polypoid and exophytic with 'nearly all' of the tumour cells contained within the polypoid projection without invading into the underlying stroma, especially in glottic and palatal tumours. Therefore, the polypoid nature of SCSC allows for almost complete elimination by the diagnostic 'biopsy,' yielding an approximate 80% 5-year survival. If recurrence develops, and a salvage procedure is necessary, a poorer prognosis can be expected. Interestingly, in laryngeal SCSC specifically, irrespective of tumour location or T-stage, there is a statistically significant better patient outcome when no epithelial marker immunoreactivity can be demonstrated (i.e. patients with tumours that are keratin immunoreactive tend to have a worse prognosis). When metastatic disease develops, cervical lymph nodes and pulmonary involvement is most frequent.

BASALOID SQUAMOUS CELL CARCINOMA

Basaloid squamous cell carcinoma (BSCC) is a high-grade variant of SCC, with a predilection for multifocal involvement of the oropharynx (base of tongue), pyriform sinus, supraglottic larynx, hypopharynx and palatine tonsil. It primarily affects men in the seventh decade of life with frequent cervical lymph-node metastases at presentation.[46–55] Macroscopically, these tumours are usually firm to hard, with associated central necrosis, occurring as exophytic to nodular masses, measuring up to 6 cm in great dimension.

Histologically, the infiltrating tumour offers a variety of growth patterns, including solid, lobular, cribriform, cords, trabeculae, nests and glands or cysts. The depth of invasion may not be obvious on a shallow biopsy, and so a generous biopsy is imperative for accurate interpretation of the neoplasm. Vascular or lymphatic perforation is common, whereas neurotropism is less frequent. Surface ulceration is frequently noted. The basaloid component is the most diagnostic feature, incorporating small, closely opposed moderately pleomorphic cells with hyperchromatic nuclei and scant cytoplasm into a lobular configuration with peripheral palisading, closely associated with or involving the surface mucosa (Fig. 6). These basaloid regions are in direct continuity with areas of squamous differentiation, including abrupt keratinization in the form of squamous pearls, individual cell keratinization, dysplasia, or squamous cell carcinoma (*in-situ* or invasive; Fig. 7). A spindled squamous cell car-

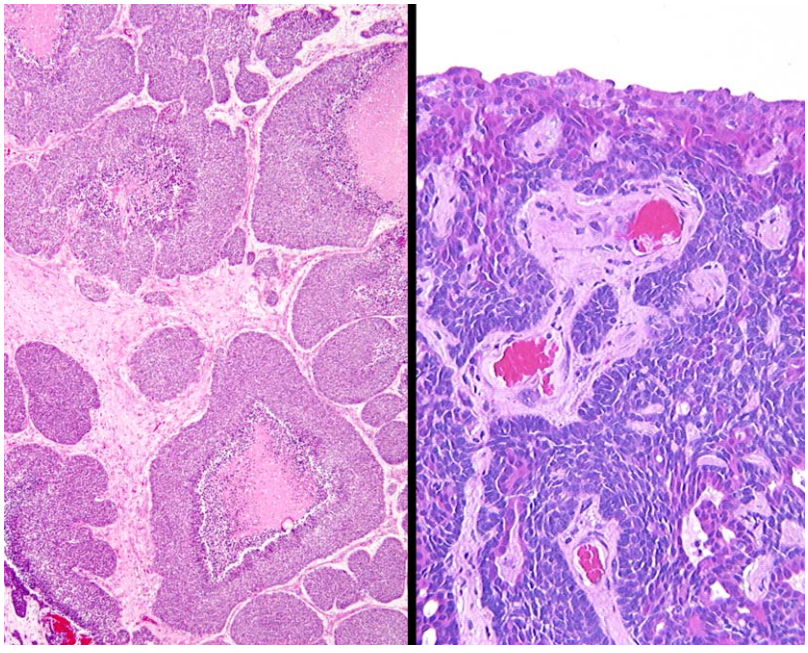

Figure 6 The neoplastic infiltrate of basaloid squamous cell carcinoma is dominated by a lobular arrangement of basaloid cells with areas of comedonecrosis (left). Areas of surface squamous differentiation are intimately associated with the basaloid component (right).

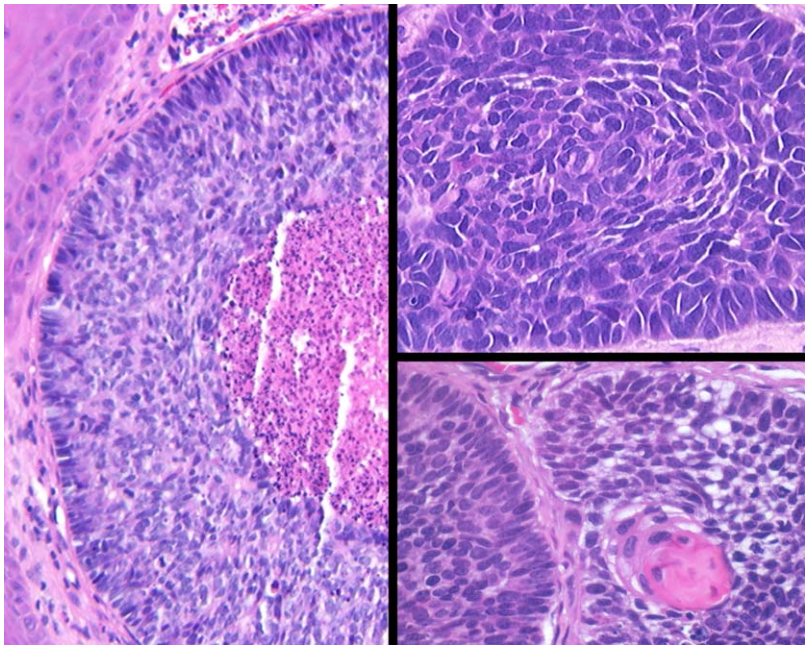

Figure 7 The surface is noted adjacent to the basaloid proliferation with central necrosis (left). Pleomorphic and hyperchromatic nuclei with high nuclear-to-cytoplasmic ratio and nuclear palisading in a BSCC (right upper). Squamous differentiation represents the minor component in BSCC and includes abrupt keratinization intimately admixed with the basaloid cells (right lower).

cinoma may also be seen in rare cases. The basaloid component frequently demonstrates marked mitotic activity as well as comedonecrosis in the centre of the neoplastic islands. The tumour cells are separated by a prominent dense pink hyaline material and small cystic spaces containing mucoid type material. The hyaline material may be arranged in a cylinder, rimmed by cells. In metastatic disease, both basaloid and squamous cell components can be seen, although the basaloid features tend to predominate.

Epithelial markers (cytokeratin, CAM5.2, epithelial membrane antigen, CK7, and 34ßE12) are consistently reactive, whereas no reaction is present with neuroendocrine markers (chromogranin, glial fibrillary acidic protein, synaptophysin).[49,51,54,55] A delicate perinuclear rim or 'dot' of vimentin immunoreactivity is described, although not always present.[48,55] Although the differential diagnosis includes neuroendocrine carcinoma (small-cell undifferentiated carcinoma), squamous cell carcinoma, adenoid cystic carcinoma, adenosquamous carcinoma, mucoepidermoid carcinoma and spindle-cell carcinoma, a correct diagnosis is predicated on an adequate tissue sample of sufficient depth in order to demonstrate the heterogeneous nature of the tumour. Adenoid cystic carcinoma does not disclose any squamous differentiation and usually metastasizes to distant sites rather than cervical lymph nodes. Adenoid cystic carcinoma usually does not have prominent pleomorphism, mitoses or necrosis. Cutaneous basal cell carcinoma may invade into the upper aerodigestive tract, but it has different histomorphologic features. When the diagnosis of a basaloid squamous carcinoma is made, there is an increased possibility of a contemporaneous primary elsewhere. Nasopharyngeal BSCC has been shown to be associated with Epstein-Barr virus, but this has not been revealed in BSCC of other head and neck sites.[54] BSCC requires aggressive multimodality therapy, including radical surgical excision, neck dissection, radiotherapy and often chemotherapy (especially for metastatic disease). Despite aggressive therapy, the overall mortality rate is high (60% die of disease).[47–55]

ADENOSQUAMOUS CARCINOMA

Adenosquamous carcinoma (ASC) is a high-grade variant of squamous cell carcinoma composed of an admixture of squamous cell carcinoma and adenocarcinoma. ASC occurs throughout the upper aerodigestive tract, often as an indurated submucosal nodule up to 5 cm in maximum dimension, although most are less than 1 cm. Most patients present with lymph-node metastases (65%).[46,56–59] By definition, the tumour demonstrates biphasic components of adenocarcinoma and squamous cell carcinoma, with an undifferentiated cellular component in several tumours (Fig. 8). The squamous cell carcinoma can be *in situ* or invasive, ranging from well to poorly differentiated. Squamous differentiation is confirmed by pavemented growth with intercellular bridges, keratin pearl formation, dyskeratosis and/or individual cell keratinization. The adenocarcinoma component can

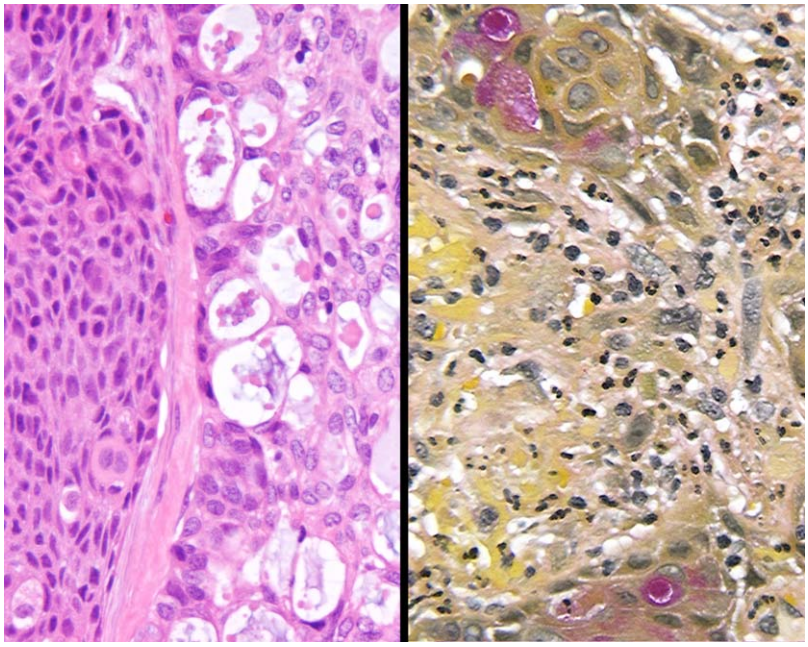

Figure 8 Adenosquamous carcinoma demonstrates blended adenocarcinoma and squamous cell carcinoma within a single tumour mass, accentuated by a mucicarmine stain (right).

be tubular, alveolar and/or glandular, although mucus-cell differentiation is not essential for the diagnosis. The cells in the adenocarcinoma can be basaloid, and separation from basaloid squamous cell carcinoma can at times be arbitrary. The two carcinomas may be separate or intermixed, with areas of commingling and/or transition of the squamous cell carcinoma to adenocarcinoma. The 'undifferentiated' areas between the two distinct carcinomas are often composed of clear cells. Both carcinomas may demonstrate frequent mitoses, necrosis and infiltration into the surrounding tissue with affiliated perineural invasion. There is typically a sparse inflammatory cell infiltrate at the tumour-stromal interface.[46,46,56–59] In contrast to BSCC, ASC shows a prominent squamous cell component, absence of basaloid cells with peripheral nuclear palisading and the presence of glandular differentiation, including intracellular and intraluminal epithelial mucin (mucicarmine positive material). Although separation of adenosquamous carcinoma from mucoepidermoid may be impossible in some cases, and it has been stated that adenosquamous carcinoma is a high-grade mucoepidermoid carcinoma,[56] a mucoepidermoid carcinoma demonstrates intermediate type cells and generally does not have true squamous cell differentiation. The demonstration of true mucus cells, with squashed, eccentrically placed nuclei, will also help segregate these neoplasms. There is no true adenocarcinoma and distinctly separate squamous cell carcinoma in a mucoepidermoid carcinoma. An adenocarcinoma with squamous metaplasia generally does not demonstrate the nuclear criteria of a malignant squamous cell component. An adenoid squamous cell carcinoma (acantholytic squamous cell carcinoma) is a variant of squamous cell carcinoma, in which there is acantholysis of the squamous cells, a few of which can be clear, mimicking glandular differentiation. A mucicarmine stain will not react, discriminating between these two tumours.[60] A contemporaneous squamous cell carcinoma and adenocarcinoma may affect the upper aerodigestive tract, but these lesions are usually temporally separated. Aggressive surgery with neck dissection yields an approximate 55% 2-year survival.

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