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Oral Squamous Cell Carcinoma Variants - A Clinico-Pathologic Relevance

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Abstract: *Squamous cell carcinoma (SCC) is the most common malignant neoplasm of oral cavity. It is also the most common malignancy of upper aero-digestive tract. Conventional type Oral SCC remains predictable for diagnosis but its variants offer diagnostic as well as prognostic challenge as they may be histopathologically benign or may mimic other malignant diseases. The common variants of SCC include Verrucous Carcinoma, Basaloid SCC and other rare variants (spindle cell, papillary, adeno-squamous). This article discusses the clinico-pathologic features of these unusual variants and their differential diagnosis for determining the accurate diagnosis as well as prognosis.*

Keywords: *Squamous Cell Carcinoma (SCC), Verrucous Carcinoma (VC), Basaloid SCC, Spindle cell Carcinoma, Papillary Squamous Cell Carcinoma.*

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I. Introduction

Squamous cell carcinoma (SCC) is the most common malignant mucosal neoplasm of head and neck accounting for over 90% of all malignant neoplasm. Oral cancer is among the 10 most common cancer worldwide. [1] In the oral cavity squamous cell carcinoma is the most prevalent neoplasm. [2]

SCC is generally divided into 3 histological categories: - in situ superficially invasive or deeply invasive carcinoma, with additional modifies based on histologic grading including well, moderate or poorly differentiated, along with the presence or absence of keratinization. SCC can be ulcerative, flat, polypoid, verrucous or exophytic. [3] Each variant has a unique histomorphic appearance which raises number of different differential diagnostic consideration. e.g. Verrucous carcinoma is milder form of SCC whereas Basaloid SCC is aggressive entity, so proper clinical and biological course should be established for diagnosis and prognosis of lesion.

This article discusses the clinico-pathologic features of conventional SCC and its variants for determining the correct diagnosis.

Oral Squamous Cell Carcinoma (OSCC)

Oral squamous cell carcinoma is usually seen in older individual. Risk factor associated are tobacco (smokeless and smoking), alcohol, betel quid, phenolic agents, radiation, iron deficiency, Vitamin-A deficiency, syphilis, environmental and occupational factors, oncogenic viruses (HPV and EBV), Candidial infection, genetic predisposition, immunosuppression. All these factors probably inherit in multifactorial process. [4,5,6]

Mucosal SCC arises anywhere in head and neck; tongue being most commonly affected site in oral cavity. Clinically SCC is can be ulcerative, flat, papillary or exophytic in growth, ranging from minute mucosal thickening to large masses.

Conventional SCC is composed of variable degrees of squamous differentiation (i.e. well, moderate and poor). Histologically SCC arises from dysplastic surface epithelium and is characterized by invasive islands and cords of malignant squamous epithelial cells. SCC shows disorganized growth, loss of polarity, dyskeratosis, Keratin pearls, intercellular bridge, an increase nuclear Cytoplasmic ratio, nuclear chromatin irregularities, prominent eosinophilic nucleoli and increase mitotic figure. [7,8] A rich inflammatory infiltrate is seen at tumor to stroma junction, along with dense desmoplastic fibrous stoma. [**figure 1**]

VARIANTS OF OSCC

A. Verrucous Carcinoma: Ackerman (1948) was first to describe and characterize Verrucous Carcinoma (VC) as distinct entity. [9] It is the most common variant of SCC seen in oral cavity, specifically at the buccal mucosa or gingiva. [10,11] This lesion occurs in older people usually in 7^{th} or 8^{th} decade of life. Oral lesion is often related to use of tobacco, alcohol, poor oral hygiene and HPV.

Clinically, Verrucous Carcinoma of mouth is characterized by a cauliflower like exophytic growth with a cleft, warty, whitish to gray surface which may have erythematous areas. [12,13]

Microscopically VC has a wart like appearance with abundant keratosis and parakeratosis arising with from a fold, acanthotic squamous epithelium which leads to noted appearance of "church spires". Advancing margins of tumor are usually broad or bulbous rete pegs with pushing rather than an infiltrative appearance. Parakeratotic crypting is common feature. [**figure 2**] Hybrid lesions seen, when tumors present the dominant microscopic features of VC, but contain small areas of tumor invasion. To diagnose Verrucous Carcinoma, ample sectioning and good representative sampling of the base of lesion are needed as evidence of invasion is required for definite diagnosis.

Verrucous hyperplasia should be differentiated from VC histologically. VC will show features of invasion with more acanthosis and broad based rete pegs extending deeply into the stromal tissue, where as VH should not extend more deeply than adjacent uninvolved epithelium. Similarly, Verruca Vulgaris has a prominent keratohyline granules and parakeratosis with sharply defined acanthotic rete ridges, features not seen in VC. [3] Papillary SCC also is mentioned occasionally as a differential diagnostic consideration. These lesions are not very similar histologically and generally should not be confused. Still there seems to be some histologic overlap in phenotype and some cases can show mixed features.

Biological behavior of VC is between non-neoplastic hyperplasia and conventional SCC. [14] Therefore, it may be helpful to think of VC as an extremely well differentiated squamous cell carcinoma.

B. Basaloid Squamous Cell Carcinoma: Basaloid Squamous Cell Carcinoma (BSCC) is a rare and high grade variant of SCC that was first identified as a separate histopathologic entity by Wain et al. [15] Usually this tumour shows predilection for base of tongue, hypopharynx and supra glottis larynx [16,17,18]. Mainly seen in older people with a history of heavy smoking and alcohol consumption. [19,20]

Clinically these tumors are firm to hard with associated central necrosis and occur as exophytic to nodular mass. [21]

Histologically tumor shows variety of growth patterns including solid, lobular, crebriform, cord, trabaculae, nests and glands or cysts. Large nests can have central comedo form necrosis. [22] The Basaloid component is 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. 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 SCC (in situ or invasion). [23,24] [**figure 3**]

Most patient present with higher stage with nodal metastases and the tumor behave as poorly differentiated SCC. Correct diagnosis of Basaloid SCC can be challenging especially with small biopsy specimen. Lack of representative sample containing Basaloid component with squamous component can be misdiagnosed as poorly differentiated SCC. Therefore, when a diagnosis of poorly differentiated SCC is established by biopsy the possibility of BSCC should not be excluded. [25] IHC analysis can be very helpful in differentiating these rare tumors. [26,27,28]

The clinical course and prognosis of BSCC have been considered worse than for conventional SCC due to its aggressive biological behavior characterized by early local or regional recurrence and distant metastases as well as lower reported survival rate. [29,30]

C. Other rare variants of OSCC: The classification adopted by the IARC-WHO included spindle cell carcinoma, papillary SCC, adenosquamous carcinoma, acantholytic SCC and carcinoma cuniculatium as the variants to be considered. [31] Even though being very rare in oral cavity, they need to be considered as separate entities, being common neoplasms of upper aerodigestive tract.

Spindle cell carcinoma:

Spindle cell (sarcomatoid) carcinoma (SCSC) is an uncommon type of SCC comprising upto 3% of SCC. [32,33] It is named because the majority of neoplastic cells that form the neoplasm show a mesenchymal (sarcomatoid) phenotype. [34] Most frequently seen in older man and commonly related to alcohol abuse and smoking of tobacco products. [35] Few cases are also associated with radiation exposure as an etiology.

Clinically the neoplasm presents as exophytic polypoid mass. Larynx is the most common location; still they can arise anywhere in upper aero-digestive tract. [36] Very rare incidence of the tumor is seen in oral cavity.

Histologically this malignancy often presents as ulceration with fibrinoid necrosis. So it may be difficult to discern the transition between the surface epithelium and spindle cell component. Mesenchymal component makes up vast majority of tumor, but if overlying epithelium is present squamous dysplasia is noted. [34] Low to moderate malignant pleomorphism is present. Mitotic figure and atypical mitotic bodies are seen. Cellular arrangement shows different pattern. [**figure 4**] Mucoepidermoid carcinoma (MEC) of minor salivary glands should be differentiated from SCSC as former have better prognosis. SCSC shows abnormalities of surface epithelium which is not seen in MEC. [37,38]

Papillary Squamous Cell Carcinoma (Papillary SCC):

Papillary SCC is uncommon, de novo but distinct variant of SCC separable from Verrucous Carcinoma (VC). Lesion occurs in older man like all other variants of SCC. [39,40] Because of its rarity the pathogenesis remains unclear, still HPV infection is related to this lesion. Most common location is larynx, followed by oropharynx and hypopharynx, very rarely seen in oral cavity.

Clinically these lesions are large exophytic and appear papillary or even warty akin to VC. Histological appearance is similar to Sino-nasal papillomas at low power. It consists of multiple thin delicate filliform, finger like papillary projections. The papillae contain a delicate fibro-vascular core surrounded by the neoplastic epithelium. Stratified squamous epithelium shows increased nuclear Cytoplasmic ration, nuclear irregularities, loss of polarity, numerous mitotic figures and also koilocytic change is noted [41] [**figure 5**]. Distinction of papillary SCC is important because these patients seem to have better prognosis when compared with location and stage matched with conventional SCC patient. Most common differential diagnosis is Sino-nasal papillomas. Differentiating factor here is Sino-nasal papilloma do not show such high grade of epithelial atypia. VC can be differentiated by lack of dysplastic features and cytomorphic atypia. Papillary variant should be differentiated from exophytic SCC as former has better prognosis. It is noted that papillary variant of SCC appears more like stalk of celery cut cross section and should not resemble cauliflower. [42]

Adeno-squamous carcinoma (ASC):

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 1cm. Most patients present with lymph-node metastases (65%). [43]

By definition, this tumor demonstrates biphasic components of adenocarcinoma and squamous cell carcinoma, with an undifferentiated cellular component in several tumors. The squamous cell carcinoma can be in situ or invasive, ranging from well to poorly differentiated. Histologically, the squamous differentiation is confirmed by pavemented growth with intercellular bridges, keratin pearl formation, dyskeratosis and/or individual cell keratinization. The adenocarcinoma component can 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. [**figure 6**] 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 tumor-stromal interface. [44]

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, and 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. An adenoid squamous cell carcinoma (**acantholytic squamous cell carcinoma**) is a variant of squamous cell carcinoma, in which there is acantholytic of the squamous cells, a few of which can be clear, mimicking glandular differentiation. A mucicarmine stain will not react, discriminating between these two tumors. [45] Thus, a conventional Squamous cell carcinoma and Adenocarcinoma both affect the upper aerodigestive tract, but these lesions should be separated.

II. Conclusion

Clinical as well as histopathologic knowledge is important to consider the correct diagnosis. SCC being most common neoplasm of oral cavity, but its variants has low frequency so clinical and biological course of variants of SCC remains challenge. Many times atypical lesions are misdiagnosed as the histologic variants which affects the prognosis of patient. Appropriate systemic approach is required for correct diagnosis. Good

sampling and multiple sections are required to ensure correct diagnosis of sub types of SCC, to provide more accurate treatment. The histopathologic features are therefore, described in detail in an attempt to allow the general surgical pathologist to separate these variants of OSCC in order to achieve appropriate clinical management.

Figures	Legends
Figure 1	Conventional OSCC
Figure 2	Verrucous carcinoma
Figure 3	Basaloid squamous cell carcinoma
Figure 4	Spindle cell carcinoma
Figure 5	Papillary squamous cell carcinoma
Figure 6	Adeno-squamous carcinoma

Table 1: Differential Diagnoses of OSCC Variants

Oral Squamous Cell Carcinoma Variants	Differential Diagnosis
Verrucous carcinoma	Verruca Vulgaris; Verrucous hyperplasia; conventional-type SCC; papillary SCC.
Basaloid SCC	Adenoid cystic carcinoma; basal cell Adenocarcinoma; other Basaloid salivary gland-type neoplasms.
Spindle cell carcinoma	Benign and malignant mesenchymal lesions; melanoma.
Papillary SCC	Benign squamous papilloma (eg, laryngeal papilloma, sinonasal papilloma); Verrucous SCC; exophytic Conventional-type SCC.

Table 2. : Comparison of clinic-pathologic relevance among OSCC Variants

	conventional Squamous cell carcinoma	Verrucous carcinoma	Basaloid squamous cell carcinoma
Clinical features	Ulcerated appearance	Cauliflower-like appearance	Ulcerated appearance
Preferential sites	Tongue Floor of the mouth	Buccal mucosa Hard palate	Base of the tongue Floor of the mouth
Histopathologic features	Variable degree of keratinization, pleomorphism and mitotic activity	Intense keratinization, compressive pattern and minimal atypia	Basaloid pattern in intimate association with a squamous component
Metastatic potential	High	Absent	High (similar to poorly differentiated OSCC)
Prognosis	Poor	Excellent	Poor (similar to poorly differentiated OSCC)

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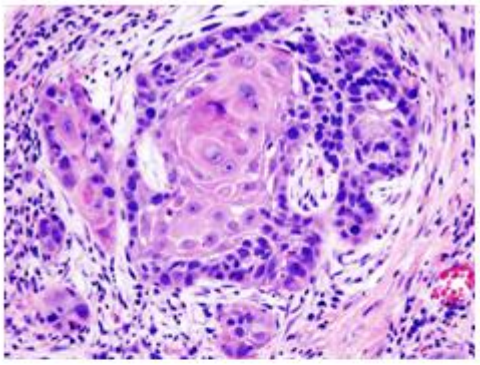

Fig .1 Conventional OSCC

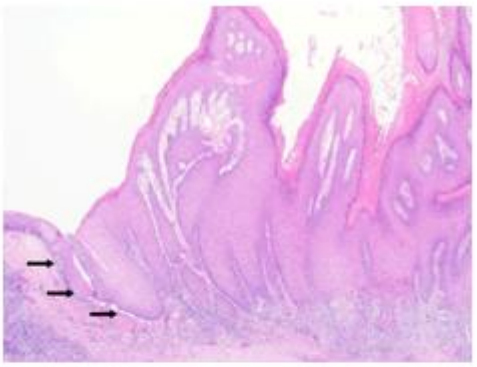

Fig .2 Verrucous carcinoma

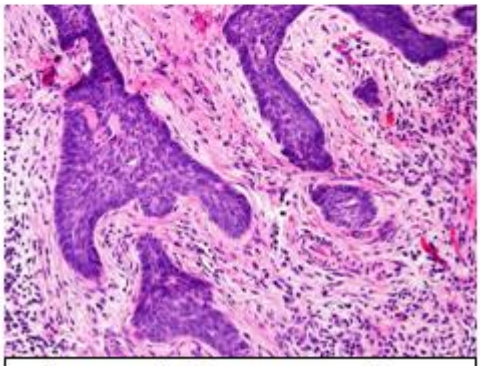

Fig .3 Basaloid squamous cell

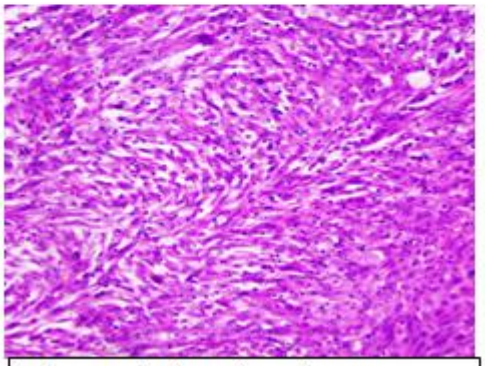

Fig .4 Spindle cell carcinoma

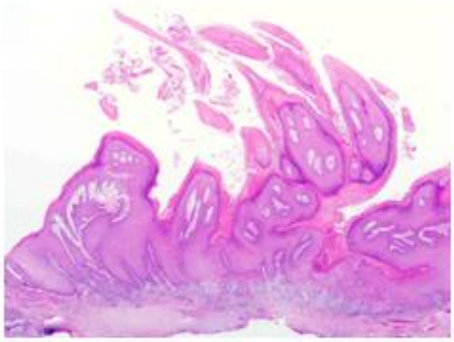

Fig .5 Papillary squamous cell

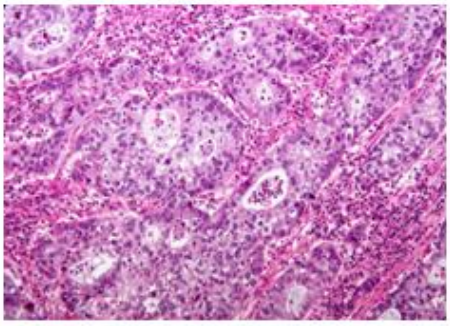

Fig .6 Adeno-squamous carcinoma

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