

HISTOPATHOLOGY OF ORAL SQUAMOUS CELL CARCINOMA – A REVIEW

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Abstract

Squamous cell carcinoma is one of the most common malignant tumor of oral cavity. Smoked and smokeless form of tobacco, alcohol, diet and immunosuppression are the main aetiological factors in oral cancers. Grading and cytomorphology of the neoplasm serve as a precise measure for predicting the outcome of the neoplasm and for treatment planning. Border was the first to initiate the quantitative grading of cancer. Histopathological grading is an important factor in determining the prognosis of oral carcinoma.

Oral squamous cell carcinoma has a high malignant potential with great propensity for metastasis to the regional lymph nodes through vascular invasion and thereby leading to loco regional failure.

Key Words: - Grading, Metastasis, Oral squamous cell carcinoma.

Introduction

Squamous cell carcinoma is one of the most common malignant tumors of the oral cavity. It comprises 90-95 % of all oral malignancies. The incidence of oral cancer is high in many countries; furthermore the intraoral location differs in different population groups.¹

Oral Squamous Cell Carcinoma (OSCC) is a disease with worldwide distribution and is one of the leading cancers in most Asian countries. The epidemiology, clinicopathological classification, and natural history of oral squamous cell carcinoma have been extensively investigated. These observations have led to better definitions of precursor and in situ neoplastic changes that have in turn contributed to a more comprehensive understanding of the etiological factors and pathobiology of development of this common cancer.²

Aetiology:-³

Aetiological factors in oral cancers are smoked and smokeless tobacco, alcohol, diet and nutrition, viruses, immunosuppression and chronic infection.

Location of oral Squamous cell carcinoma:-^{2,4,5}

SCC of the head and neck possesses unusual features not universally found in carcinomas in other anatomic sites. SCC is a field-defect phenomenon. Field defect means that, if dysplastic changes occur in 1 location of an organ or body site, other locations in the same organ are likely to have dysplastic changes.

Histopathology:-

Squamous cell carcinoma arises from the dysplastic surface epithelium. The various cytological and architectural features described to grade epithelial dysplasia are: -^{2,3,6}

1. Drop shaped rete pegs
2. Disturbed polarity of the basal cells
3. Basal cell hyperplasia
4. Irregular epithelial stratification or Disturbed maturational sequence
5. Cellular pleomorphism/anisocytosis
6. Nuclear hyperchromatism

7. Prominent nucleoli
8. Increase in nuclear cytoplasmic ratio
9. Increased mitosis and Abnormal mitosis
10. Loss of cellular adhesion and cohesion
11. Intraepithelial keratinization

Acantholytic (Adenoid) Squamous cell carcinoma^{2,3,6,7}

Adenoid Squamous cell carcinoma is included in the world health organization (WHO) classification of upper respiratory tract tumors and defined as an Squamous cell carcinoma in which pseudoglandular spaces or lumina result from acantholysis of tumor cells.

Microscopically, the tumor is characterized by a lobular growth pattern of keratinizing Squamous cell carcinoma that shows central regions containing rounded spaces. (Pseudoglandular alveolar areas that are lined by a basal layer of polygonal cells with the central lumina containing detached dyskeratotic acantholytic neoplastic cells, “glassy” keratinocytes).

Verrucous carcinoma^{2,3,6,7}

Verrucous carcinoma is a low grade Squamous cell carcinoma first described in 1948 as occurring in the oral cavity. It is slow growing, at first exophytic, verrucous, and fungating tumor that may ultimately penetrate deep into the tissue. However, it causes regional metastasis only very late, if at all.

Histologically, verrucous carcinoma is broad based and invasive, with plump papillary invaginations of thickened and infolding epithelium that lack the usual cytological criteria of malignancy. The superficial portions generally resemble a verruca by showing hyperkeratosis, parakeratosis, and acanthosis. The keratinocytes appear well differentiated, stain lightly with eosin, and possess a small nucleus. The tumor invades with broad strands that often contain keratin-filled cysts in the centre. There are large, bulbous, downward proliferations that compress the collagen bundles and push them aside

Spindle cell carcinoma^{2,3,6,7}

Spindle cell carcinoma also called as pseudocarcinoma, Sarcomatoid Squamous cell carcinoma, ‘collision tumor’ or

sarcamatooid carcinoma, is a biphasic tumor SCC cells and pleomorphic spindle cells.

Histopathology:-

Spindle cell typically exhibits areas of Squamous cell carcinoma and areas of spindle cells. The former component may be very scant or limited to noninvasive areas of epithelial dysplasia or carcinoma in situ located at the surface of the tumor, and its identification may require extensive sampling for histologic examination. The pleomorphic spindle cells usually form the bulk of the lesion, they are arranged in fascicles or whorls. Storiform, myxoid, microcystic, or giant cell areas may also be present. Foci of osteoblastic or chondroblastic differentiation (both benign and malignant) is seen.

Basaloid SCC^{2,3,6,7}

Basaloid SCC is less common than conventional SCC of the head and neck and was first characterized in the upper aerodigestive tract in 1986 by Wain et al.

Histopathology:-

Almost all basaloid SCCs have regions with conventional SCC. In addition, they have a follicular or lobular pattern of invasion, with peripheral, slightly elongated, palisaded cells surrounding each lobule. The lobules often contain central necrosis with visible necrotic material. At other times the central material completely "drops out," giving a pseudoglandular appearance. Basaloid component of the of the component of the tumor is defined by four features :-

1. Solid growth 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
4. Small cystic spaces containing material resembling mucin that stains with periodic acid-schiff or Alcian blue

Papillary SCC^{2,3,6,7}

Papillary SCC is uncommon but certainly merits discussion because of the confusion it may cause the pathologist and surgeon.

On histology, in situ or invasive papillary SCCs have similar architectures. They contain benign, fibrovascular cores with overlying squamous epithelium. The epithelial layer may be keratinizing or nonkeratinizing and, with in situ lesions, full-thickness atypia is present. Koilocytotic atypia is defined as nuclei with perinuclear halos where the nucleus itself is twisted with bilobed to multilobed outlines and where indentations of nuclear contour are frequent. This particular form of cellular distortion is well related to HPV infection of the cells.

Mucin producing Squamous cell carcinoma^{2,3,6,7}

This rare variant of Squamous cell carcinoma is associated with a more aggressive clinical course than the most cutaneous Squamous cell carcinomas. Different designations have been given to such type of carcinomas

such as mucoepidermoid carcinoma and adenosquamous carcinoma of the skin.

Mucoepidermoid carcinoma^{2,3,6,7}

Although mucoepidermoid carcinoma is a neoplasm of the salivary glands, it occurs in most of the locations in the upper aerodigestive tract where SCCs and their variants occur. As the name implies, mucoepidermoid carcinoma is a malignant epithelial neoplasm with both mucus producing cells and epidermoid (ie, squamous) cells. These 2 cell types are present in various tumors in different proportions. The ratio of these cell types is the criterion for grading the malignancy. The higher the percentage of squamous cells, the higher the grade of the tumor. Technically, a third cell type, the intermediate cell, is also present in mucoepidermoid carcinoma. Low-grade tumors are slow growing, High-grade tumors are rapidly growing masses that do produce pain with or without ulceration. Intermediate-grade tumors are slightly more aggressive than low-grade tumors but have a growth rate closer to that of low-grade tumors than that of high-grade tumors.

Adenosquamous carcinoma^{2,3,6,7}

Adenosquamous carcinoma is a rare and controversial neoplasm that, as the name implies, possesses histomorphologic features of an adenocarcinoma and Squamous cell carcinoma.

Histopathology:-

The gross description of these lesions has been of erythroplakic ulcerated area to a polypoid broad based mass. Histopathologically, the tumor component is composed of an admixture or separate areas of SCC and adenocarcinoma.

The Squamous epithelium required two of the following features:-

1. Intercellular bridging
2. Keratin pearl formation
3. Parakeratotic differentiation
4. Individual cell keratinization and
5. Cellular arrangements showing pavement or mosaic pattern.

The glandular epithelium required the demonstration of intracytoplasmic sialomucin by high iron diamine alcian blue or PAS stain retention after diastase digestion and Mayer's mucicarmine. The tumor cells were of three basic types:

1. Basaloid cells
2. Squamous cells
3. Undifferentiated cells

Lymphoepithelioma^{1-3,6,7}

Lymphoepithelioma also called lymphoepithelial carcinoma is a histological variant of SCC that was first reported by Regaud Reverchon and independently by Schmincke. At present it is defined by the occurrence of a distinctive

intermingling of undifferentiated carcinoma cells with a prominent lymphoid stroma .

Microscopically, the nuclei are pale, oval or round ,may show prominent nucleoli and smooth nuclear membrane. Frequently, spindle shaped tumor cells with hyperchromatic nuclei are present. The associated infiltrate is mixed and composed of T – Lymphocytes and may contain plasma cells, follicular dendritic cells, or abundant eosinophils.. There may also be presence of noncaseating granulomas negative for acid-fast bacilli, sarcoid like granulomas and localized amyloid.

Nasopharyngeal Squamous cell carcinoma^{2,3,6,7}

All forms of nasopharyngeal carcinoma are derived from the surface epithelium of the nasopharynx, having ultrastructural features such as tonofilaments and desmosomes of Squamous cell carcinoma

WHO classification of nasopharyngeal carcinoma.^{2,3,6,7}

World health organization (1978)

1. Squamous cell carcinoma (WHO type I)
2. Non-keratinizing carcinoma (WHO type II)
3. Undifferentiated carcinoma (WHO type III)

World health organization (1991)

1. Squamous cell carcinoma
2. Non-keratinizing carcinoma
 - A. Differentiated non-keratinizing carcinoma
 - B. Undifferentiated carcinoma.

Grading of oral Squamous cell carcinoma

The histologic grading of Squamous cell carcinoma represents an estimation of pathologists of the anticipated biological behavior of the neoplasm. Various grading systems over the years have been published which are as follows:-

Broder was the first to initiate the quantitative grading of cancer based on the proportion of the neoplasm resembling normal Squamous epithelium. But there was lack of correlation between the degree of differentiation and prognosis.⁹

Mc Gavaran et al reported significant correlation between the frequency of metastasis and type of invasive growth pattern in a study on Squamous cell carcinoma of larynx. They identified two distinct types – one having ‘pushing’ and the other ‘infiltrating’ margin.⁹

A study was done by Eneroth et al in Squamous cell carcinoma of palate in 123 patients wherein they graded the tumors into highly and poorly differentiated. Carcinomas with well-defined cords and strands of neoplastic epithelial cells, as well as neoplasms that showed keratinization, were recognized as highly differentiated carcinomas and carcinomas with diffuse growth, little or no tendency to form cords and no evidence of keratinization were classified as poorly differentiated carcinomas.¹⁰

Later after a year, the multifactorial malignancy system was developed by Jakobsson et al.¹¹ They emphasized that histological relationship of the neoplasm to the surrounding host tissue also to be taken into account. This system included following parameters in the grading – morphological parameters structure tendency to keratinization, nuclear aberrations, number of mitosis and evaluation of tumor host relationship as estimated by the parameters, ‘mode’ and ‘stage of invasion’, ‘vascular invasion’ and the ‘degree of lymphoplasmocytic infiltration’. This system of classification was found to be better in predicting 5 year result than the TNM classification.

Grading system by Jakobbsen was developed by Fisher. He indicated that the malignancy grade of biopsy tissue tend to be lower than the definitive sections obtained from the surgical specimen.¹²

Histopathological grading system was also further developed by Jakkobson et al was developed by Lund et al. He introduced a histological score defined as the sum total of points divided by the number of parameters evaluated. A statistically significant correlation was found was found between the microscopic score and death rate as well as the frequency of local recurrences and regional lymph node metastasis in a study done on Squamous cell carcinoma of the lip in a series of 438 patients.¹³

This modified grading system was reviewed by Helweolarsen et al in a study of 52 patients with carcinomas of larynx. No significant correlation was found between histological grade and clinical course of disease. Poor prognostic reproducibility was also reported.¹⁴

Grading system developed by Jakobsson et al was again modified by Anneroth and Hensen¹⁵ for application to ssquamous cell carcinomas of the tongue and floor of the mouth. Omission was done for the one of the parameters ‘vascular invasion’. Reproducibility of the system was found to be good in statistical analysis.

Crissman et al¹⁶ made second modification of grading system in a study of 77 patients with Squamous cell carcinoma of the oropharynx. Treated formerly with preoperative radiation therapy followed by surgery. Deletion was done for ‘stage of invasion’ and possible or probable vascular invasion. The results indicated that the parameter, ‘pattern of invasion’ was the single most important histological variable in predicting survival.

Jakobsson et al ‘s criteria was modified by Yamamoto et al¹⁷ on the basis of parameter ‘mode of invasion’ in a study done on Squamous cell carcinoma of oral cavity in 102 patients. Grade 4 was subdivided into two grades, 4C and 4D. Grade 4C described a cord like type of invasion, while grade 4D involved a widespread type of diffuse infiltration of single and/or small groups of neoplastic cells. The study showed a low frequency of metastasis in grades 1 and 2 of ‘mode of invasion’ while a high frequency was found in grades 4C and 4D, i.e. the more invasive the carcinoma, the more frequent was the metastasis formation.

Histopathological prognosticators in oral Squamous cell carcinoma

Histopathological negative prognostic factors in head and neck squamous cell carcinoma:-⁸

1. Increasing (p) TNM classification: size of primary tumor, number/laterality of positive nodes, size of largest node.
2. Vascular invasion.
3. Perineural growth.
4. Involved resection margins, e.g., less than 5mm is considered "close margins" in oral cancer.
5. Increasing tumor thickness.
6. Invasive front, i.e., infiltration of the submucosa.
7. Loss of differentiation.
8. Endophytic worse than exophytic growth pattern.
9. Field cancerization.
10. Increasing mitotic index.
11. Presence of extracapsular spread in metastatic lymph nodes

Histopathological Grade

Histopathological grading is an important factor in determining the prognosis of oral Squamous cell carcinoma. The most important and acceptable parameter is 'invasive front grading' in predicting nodal metastasis, local recurrence and survival. Grade 1 tumors have a well-defined edge composed of broad, bulbous bands and islands of tumor cells while grade 4 tumors consist of single, non-cohesive tumor cells, which form an ill-defined edge often with satellite islands well ahead of the main tumor front.¹⁸

Conclusion

Oral Squamous cell carcinoma has a high malignant potential with great propensity for metastasis to the regional lymph nodes through vascular invasion and thereby leading to locoregional failure. Various histopathological prognosticators such as vascular invasion, perineural invasion, bone involvement and lymph node involvement help in predicting the outcome and the behavior of Squamous cell carcinoma. Proper recognition of the histological variants is an important factor in treatment of Squamous cell carcinoma as verrucous carcinoma requires less aggressive treatment than as compared to conventional Squamous cell carcinoma.

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