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Histological Variants of Oral Squamous Cell Carcinoma- A Review

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Introduction

Incidence of squamous cell carcinoma (SCC) is increasing worldwide and is also expected to rise more in coming decades at an alarming rate as feared by the World Health Organization (WHO).[1] It is the most common malignancy to affect the head and neck region, accounting for approximately more than 90% of all oral malignancies.[2] The main reason behind the increased morbidity and mortality associated with this disease is the lack of awareness in the normal population about the lesion, however early diagnosis is the key to manage the disease as well as reduce the mortality.

From the histopathological point of view there are many types of SCC, ranging from indolent tumors to very aggressive tumors, with high invasive potential.[3] It has been histologically classified as: in situ, well-differentiated, moderately differentiated, and poorly differentiated.[3][4] Most author recognizing the value of conventional oral SCC (OSCC) classification on the basis of histology alone is controversial, as it is poorly correlated with outcome and response to treatment.[1]

Conventional OSCC can be presented as several variants that make up in aggregate about 10-15% of all SCC.[2] Each variant of OSCC has a characteristic histologic appearance and biological behavior which raises number of different differential diagnostic lesions into consideration e.g. Verrucous carcinoma is milder form of SCC whereas Basaloid SCC is an aggressive entity.[4] So, proper clinical and biological course should be established for diagnosis and prognosis of the lesion.

This review includes a brief overview of histologic subtypes of OSCC, emphasizing the importance of microscopic diagnosis of these variants, which in turn has an important clinical implications for the prognosis of the tumor.

Oral Squamous cell carcinoma

Oral squamous cell carcinoma (OSCC) is usually seen in the males, middle to later decades of life, although any age can be affected. The most important risk factors are, tobacco (smokeless or smoking), betel quid and alcohol, although susceptibility (immunologic factors and age), to environmental and occupational factors may also play a role. Human papilloma virus (HPV) and Epstein- Barr virus (EBV) are also linked to the development of SCC, although association versus direct effect remains unclear. No doubt all of these factors probably interact in a multifactorial process.[5]

OSCC arises anywhere in the head and neck region, although tongue is most commonly affected in the oral cavity, followed by the floor of the mouth, the gingiva and alveolar mucosa.[1][5][6] Clinically, it may resemble a leukoplakia, a verrucous leukoplakia, an erythroleukoplakia or an erythroplakia, any of which may eventually develops into a painless necrotic looking ulcer with irregular, raised indurated borders, or into a broad based exophytic mass with a surface texture which may be verrucous, pebbled or relatively smooth. When traumatized, OSCC bleeds readily, often becomes superficially secondarily infected and becomes painful. Large lesions may interfere with normal speech, mastication or swallowing. [7]

Histologically, SCC arises from dysplastic surface epithelium and is characterized by invasive islands, cords and strands of malignant squamous epithelial cells. SCC shows features like disorganized growth, loss of polarity, dyskeratosis, keratin pearls, an increased nuclear to cytoplasmic ratio, nuclear chromatin irregularities, prominent eosinophilic nucleoli and increased mitotic figures (including atypical forms). More mitotic figures and necrosis tend to appear as the grade of the tumor becomes more poorly differentiated. A rich inflammatory cell infiltrate (usually of lymphocytes and plasma cells) is seen at the tumor stroma interface, along with a dense, desmoplastic fibrous stroma. Only poorly differentiated SCC have an enigmatic resemblance to squamous epithelium, with only rare foci of squamous differentiation. Therefore, in poorly differentiated type of OSCC special studies are sometimes needed to document the epithelial nature of the tumor. Perineural invasion can be appreciated, with a positive correlation to metastatic potential. [5][8]**[Fig1].**

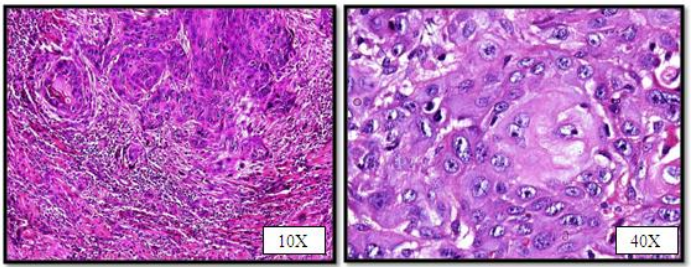

Fig 1- Conventional OSCC (Moderatly differentiated OSCC) – Invasion of malignant epithelial cells into the connective tissue showing features like hyperchromatic nuclei, altered nuclear to cytoplasmic ratio, nuclear & cellular pleomorphism, vesicular nuclei with prominent nucleoli, individual cell keratinization.

Variants of OSCC

Verrucous carcinoma

Verrucous carcinoma (VC) is described as a distinct, diagnostically challenging squamous cell neoplasm involving the oral cavity.[9][10][11] It is a rare variant of well-differentiated squamous cell neoplasms.[12] that lack conventional cytologic features of malignancy and has some unique characteristics like slow locally destructive growth and rarely intraoral and extraoral metastasis.[9][10]

In the oral cavity, VC constitutes 2% to 4.5% of all forms of SCC seen mainly in men older than 50 years.[9] The etiology of VC is not well defined, although smoking seems highly associated with the development of VC in the oral cavity. Poor oral hygiene, presence of oral lichenoid, and leukoplakic lesions may act as predisposing factors.[13] According to recent studies, human papillomavirus (HPV) could have a potential role in the tumoral development and progression, although this topic is still under discussion.[11]

Clinically, Oral VC (OVC) presents as painless, tan to white, exophytic growth, rarely exceeding 10 cm in its greatest dimension, usually presenting as cauliflower-like and pebbly mamillated warty lesions with a broad base

attachment.[14][15] The most common sites of oral cavity are buccal mucosa, followed by the mandibular alveolar crest, gingiva, and tongue.[13] Extraorally, it can occur in any part of the body, a common site being the anogenital region.[9] VC is considered to be of good prognosis because it is a tumor with predominantly horizontal growth, it tends to erode more than infiltrate. It does not present with remote metastasis.[9] Therefore, application of strict morphologic criteria is essential for the diagnosis of VC.

Histologically, VC are characterized by a hyperplastic epithelium with abundant, superficial keratinization, often forming ‘‘church spires’’ of orthokeratotic or parakeratotic squamous cells extending upward from the surface. Neoplastic cells shows minimal or no pleomorphism of cells and no mitotic activity above the basal and suprabasal layers of the epithelium. If focal atypia or dysplasia is evident, it must be limited to the basal layer of epithelium.[14] Cells have abundant eosinophilic cytoplasm, which generally undergoes uniform keratinization as the cells migrate up towards the surface. Individual cell keratinization (dyskeratosis) and keratin pearl formation may be focally seen.[10]

The broad bulbous rete ridges show “elephant feet-” like endophytic growth pattern with pushing borders, infiltrating at the same depth and seems to compress the underlying connective tissue. The epithelium is well differentiated in all the rete pegs. Abrupt transition from normal epithelium to endophytic ingrowth is taken as an important parameter to differentiate it from benign verrucous growths.[11][14] The endophytic growth that is a hallmark of this tumor is due to its resilient basement membrane (BM) that probably acts as an effective barrier to prevent the carcinomatous growth.[14][15] Lymphoplasmacytic inflammatory host reaction is marked, especially in cases where keratin has plunged deep into the connective tissue.[14]

VC should be analysed regarding conventional SCC, especially with those SCC showing “verrucoid” features, proliferative verrucous leukoplakia (PVL), verrucous hyperplasia, pseudoepitheliomatous hyperplasia, verruca vulgaris, and keratoacanthoma when VC affects cutaneous sites.[1] The increased thickness of the infiltrative epithelial component in comparison to that of adjacent normal epithelium is of assistance to separate VC from verrucous hyperplasia whilst the lack of papillary projections and cytological atypia separate it from papillary SCC.[16]

Up to 20% of VCs harbour areas of conventional SCC, the possibility of which, requires adequate tumor sampling due to prognostic differences between these two subtypes.[16] In cases with a long tobacco habit history, non-tender or fixed locoregional lymph nodes, infiltration by small, irregular nests of cells, vascular invasion, and perineural invasion, it becomes mandatory to rule out SCC.[14]

Although adequate surgical excision along with chemotherapy alone or in combination with radiotherapy without neck dissection is the treatment of choice for VC because, by definition these tumors lack nodal metastases. According to the literature, radiotherapy is contraindicated in the treatment of VC for the occurrence of Radiation-induced anaplastic transformation, manifesting 2 to 8 months following the therapeutic cycle.[1][10][11] Cervical adenopathy may be associated with VC, representing reactive changes and not metastatic disease.[11]

Spindle cell carcinoma

Spindle cell carcinoma (SpCC) is a high malignant variant of SCC and is a biphasic tumor of epithelial origin. Incidence of SpCC is reported of being less than 1% of all

tumors of oral cavity.[17] This tumor has been called by various other names like sarcomatoid carcinoma, carcinosarcoma, pseudosarcoma, pleomorphic carcinoma and polypoid carcinoma. Multiplicity in its nomenclature indicates the complexity of its histogenesis.[18]

Three principal theories have been proposed to explain the histogenetic nature of spindle cells. The first theory states that spindle cells and epithelial cells arise simultaneously from separate stem cells, deserving the name collision tumor. The second theory explains the nature of the spindle cell component as an atypical reactive proliferation of the stroma, and hence named pseudo sarcoma. Recently, monoclonal hypothesis is widely accepted and has been strongly supported by some studies. According to this theory, cells of both spindle and epithelial components have the same monoclonal origin, and dedifferentiation or transformation to spindle cells occur.[17][18][19]

Clinically, SpCC mostly manifests as a rapidly growing exophytic, polypoidal mass or non-healing ulcer.[20] Most of the cases are present in males between the sixth and eighth decade of life, with a clinical record associated with alcohol abuse, smoking and radiation exposure.[21] Clinical features are similar to those of their conventional squamous counterparts with the exception that many SpCCs present at low stage and are thus less likely to present with metastatic disease. On Gross sectioning, the mass is typically firm and tan or white.[10]

The classical histological picture of SpCC typically exhibits areas of SCC and areas of spindle cells. There is sharp borders between SCC areas and spindle cell component and/or gradual transition with the SCC cells dropping off from epithelial nests into spindle cell areas may be seen.[22] Most tumors are low to moderately cellular and have a storiform growth pattern, although a more-fascicular or ‘‘solid’’ appearance may predominate.[10] The spindle shape of the tumor cells has been considered to be caused by the lack of expression of cell adhesion molecule, such as cadherins and the consequent alteration of keratin filament network.[19]

The tumor 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. Pleomorphism is often mild to moderate, without a severe degree of anaplasia. Giant cells of a variably type and mitotic figures, including atypical forms, can be seen scattered throughout the neoplasm.[5] Foci of osteoblastic or chondroblastic differentiation (both benign and malignant) is seen.[23] At times, the area of elongation and spindling seems to arise from the basal epithelial cells, making it difficult for any demarcation between the surface epithelial origin and the underlying tumor.[5]**[Fig 2]**

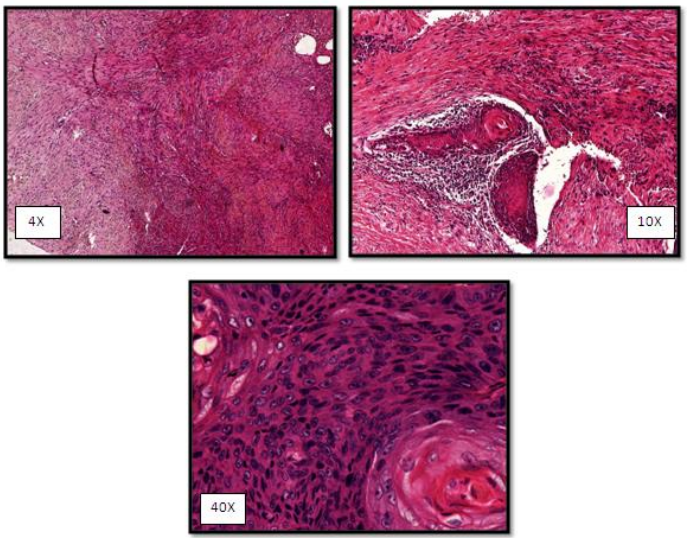

Fig 2- Spindle cell carcinoma - both epithelial cells and sarcomatoid or spindle cells are seen arranged in an interlacing fascicles. Islands of malignant epithelial cells and keratin pearl formation can be seen at places

SpCC pose a significant diagnostic challenge to the pathologist with remarkable morphological and immunohistochemical overlap with other benign and

malignant spindle cell tumors. An accurate diagnosis of these tumors is essential as they vary in their clinical management and outcome.[24]

Immunohistochemical studies are useful to differentiate between SpCC and other spindle cell tumors. Differential diagnosis ranges from benign to malignant lesions, such as fibromatosis, reactive epithelial proliferations, fibrosarcoma, rhabdomyosarcoma, fibrous histiocytoma, malignant fibrous histiocytoma, leiomyosarcoma or malignant peripheral nerve sheath tumor and malignant melanoma.[17] Immunohistochemistry has a role in confirming the diagnosis of SpCC. The sarcomatoid cells usually co-express vimentin and cytokeratin although expression of other mesenchymal markers is present to a lesser extent. Adequate tissue sampling in order to demonstrate origin from overlying epithelium is thus essential.[16]

Wide surgical excision, with or without radical neck dissection, seems to be the most preferred and successful therapeutic modality. Radiotherapy, although considered to be ineffective by most authors, is an acceptable alternative for inoperable patients as well as for those in which the surgical margins are positive or in patients with nodal metastasis.[18]

Prognosis of SpCC is dependent on location, size, and depth of invasion of tumor, stage of disease, and the presence of any keratin staining in the spindle cells. SpCC of the oral cavity and oropharynx is potentially aggressive and tends to recur and metastasize easily.[18]

Basaloid Squamous cell carcinoma

Basaloid squamous cell carcinoma (BSCC) is a rare and high grade, aggressive variant of SCC. The clinical features of BSCC are generally similar to those of conventional SCC. However, distinguishing features include a strong predilection to involve the base of the tongue, pyriform sinus, supraglottic larynx, and palatine tonsil and a tendency to present as advanced lesions.[10]Patients with head and neck BSCC more often have cervical lymph node involvement and distant metastasis. Incidence of BSCC is estimated to be 2% of all head and neck SCCs and 5% of all node-positive SCCs.[25]

It primarily affects men in the seventh decade of life.[5] The majority of cases are located within the posterior region of the oral cavity.[16] BSCC is believed to arise from a totipotential primitive cell in the basal layer of the surface epithelium or from the salivary duct lining epithelium.[26]Some authors also believe that “basaloid” pattern occurring anywhere in the body represents an attempt at glandular differentiation.[27]

Clinically, patients have similar presentation to conventional SCC such as painless irregular mass (verrucous or smooth), firm to hard, and may or may not be ulcerative measuring up to 6 cm in greatest dimension. [28][29] Etiology and pathogenesis of BSCC is similar to conventional SCC.[28]

Recent investigations have shown an association between human papilloma virus (HPV) and BSCC, particularly HPV type 16. It has also been suggested that BSCC may be a heterogeneous entity, with the subset of BSCC associated with HPV having a more favorable prognosis than those that are not.[25]

Histologically, BSCC shows unique bimorphic patterns: basaloid and squamous components with predominant basaloid components, arranged in diverse growth patterns, which include lobular, solid, cribriform, trabecular, cords, nests, and cysts or glands, focally connected to the surface epithelium. Neurotropism is seen rarely, but lymphatic and vascular perforations and surface ulcerations are commonly noted. The important diagnostic feature is the basaloid component, demonstrating closely opposed pleomorphic cells with hyperchromatic nuclei and scanty

cytoplasm arranged into a lobular pattern with peripheral palisading cells. Comedo necrosis is frequently noted in the centre of the neoplastic islands. The basaloid regions are continuous with the regions of squamous differentiation, together with abrupt keratinization in the form of squamous pearls, individual cell keratinization, dysplasia or SCC. Rarely, areas of spindled SCC may also be seen. The tumor cells are divided by a prominent thick hyaline material with small cystic spaces having mucoid-type material (which stains with periodic acid-Schiff). In metastatic disease, both basaloid and squamous cell components can be appreciated, but predominantly, basaloid features are seen.[8][29]**[Fig 3]**

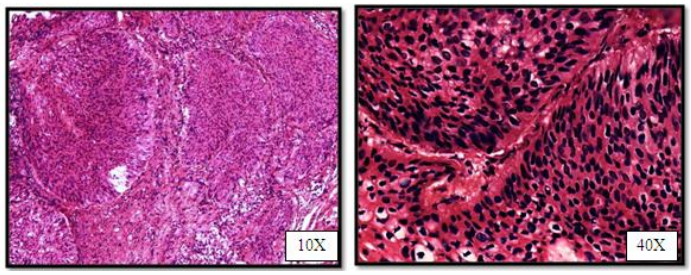

Fig 3- Basaloid Squamous cell carcinoma – Nests and follicles of basaloid cells separated by thin fibrous septa. Follicles are lined by tall columnar cells arranged in palisaded pattern. These cells show basal cell hyperplasia, hyperchromatic nuclei and nuclear pleomorphism at places. Cells located in the centre are oval to polygonal in shape.

The distinctive histologic feature of this neoplasm is its appearance as an SCC in intimate relation with a basaloid component. BSCC should be histologically differentiated from solid adenoid cystic carcinoma, adenosquamous carcinoma, mucoepidermoid carcinoma, neuroendocrine carcinoma, basal cell and polymorphous low-grade adenocarcinoma, small cell undifferentiated carcinoma, conventional SCC, basal cell carcinoma, spindle cell carcinoma and adenoid SCC.[29]BSCC shows reactivity to cytokeratin, epithelialmembrane antigen, neuron-specific enolase and to a lesser degree, carcinoembryonic antigen and S100 protein.[26]

When compared to conventional SCC, BSCC have more clinically aggressive behavior, poorer prognosis and survival rate. Survival rate of BSCC is less than half of conventional SCC. Local recurrencesof BSCC is less, but distant metastasis is about six times higher than conventional SCC. No standard treatment protocol universally. In resectable lesions with no evidence of metastasis, complete surgical excision, supplemented by postoperative radiotherapy is considered most accepted and in cases with metastasis combining systemic chemotherapy with locoregional radiation is a logical approach to treatment.[28]

Adenoid (acantholytic) squamous cell carcinoma

Adenoid squamous cell carcinoma (ASCC) accounts for 2%-4% of all SCC cases.[30] It arises most commonly in sun exposed skin areas, including the skin of head and neck region. [10][31] ASCC has derived its name from the pseudoglandular or pseudoluminal appearance resulting from acantholysis and degeneration within the islands of SCC. This change may be seen focally in otherwise typical SCCs from any anatomic site but rarely dominates the histologic appearance.[10][30] Lesions of Head and Neck have been documented involving the oral cavity, larynx, sinonasal tract, and nasopharynx. Initially, the tumor was thought to arise from sweat glands. Later subsequent studies stated that the tumor is a variant of SCC of non-eccrine origin.[30]

Oral ASCC documented more frequently in men with the peak incidence in the sixth decade of life[30] and have been described as ulcerated, nodular, indurated, warty, exophytic, keratotic, or crusted growth. Tumors often measure several centimeters, with a tan or tan-white cut surface.[10]ASCC is also known as pseudoglandular SCC, SCC with glandlike (adenoid) features, angiosarcoma like

SCC, adenoacanthoma, pseudovascular adenoid SCC and pseudoangiosarcomatous carcinoma.[31]

Histologically, these tumors are composed of alveolar or glandlike spaces lined by a peripheral layer of flattened, cuboidal or ‘‘hobnail’’ neoplastic cells. These neoplastic cells shows features like central lumina consists of detached single cell and cell aggregates of dyskeratotic or acantholytic neoplastic cells, “glassy” keratinocytes. This finding is associated with loss of immunohistochemical expression of E-cadherin, causing loss of cell adhesion in the center of the tumor nests.[31] The nuclei of the neoplastic cells are pleomorphic, often hyperchromatic with occasional extremely bizarre, large or multinucleated cells. Cytoplasm varies from scant to prominent and when present, is typically eosinophilic. Mitotic figures are frequently encountered. Sometimes acantolytic cell shows keratinization and mucous metaplasia.[8][10] Glandular pattern in ASCC includes mucous production that can be demonstrated clearly by mucicarmine stain.[30] The intervening connective tissue is very minimal, exhibiting moderate vascularity and minimal chronic inflammatory cell infiltrate. [8][10]**[Fig 4]**

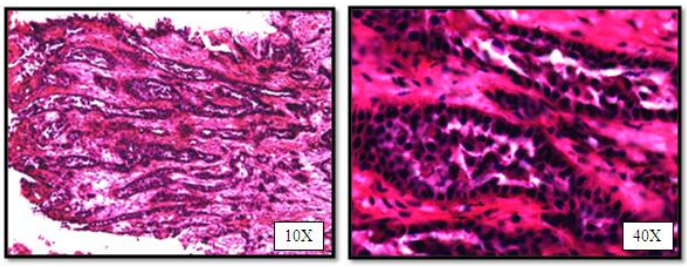

Fig 4- Adenoid squamous cell carcinoma - Characterized by presence of malignant epithelial cells in the form of tubules showing an adenoid appearance due to acantholysis. These tubules are lined by single layer of cuboidal cells.

ASCC of the oral cavity was positive forCK7, CK8, CK19, E-cadherin, and p53 but negativefor vimentin, CK20, and S100 protein. The tumor must be differentiated from SCC, adenosquamous carcinoma, basaloid SCC and some salivary gland tumors such as adenoid cystic carcinoma and mucoepidermoidcarcinoma.[32]

ASCC arising in sun-exposed areas of skin frequently have a slightly greater risk of recurrence and metastasis than conventional SCC. The pattern of disease spread is analogous to that of conventional SCC and is dominated by involvement of regional lymph nodes early in the clinical course, with distant dissemination occurring later. It has been suggested that intraoral ASCC are more aggressive with possible poor prognosis. Therefore, clinicians should consider multidisciplinary treatment. Prognosis of mucosal lesions are however controversial.[10] [30]

Adenosquamous carcinoma

Adenosquamous carcinoma (ASC) is rare and highly malignant neoplasm, which is characterized microscopically by the simultaneous presence of both true adenocarcinoma and SCC with the two components occurring in close proximity, but are generally distinct.[16][33] There are controversies about the exact histogenesis of ASC. One of the hypothesis is that neoplasm arises from carcinoma in situ of minor salivary glands and ductal epithelial tissues. However, recently, authors have strongly suggested that oral ASC is derived only from the squamous superficial epithelium, without the participation of minor salivary glands.[34]

It is also consideredas a controversial tumor, as it is similar to salivary gland mucoepidermoid carcinoma (MEC), but Evans in 1984 highlighted the worse prognosis of ASC of Head and Neck over high-grade MEC and proposed that ASC should be considered as a distinctive neoplasm.[35] In the head and neck region, larynx is the most common site of occurrence for ASC followed by the oral cavity. Within the oral cavity, the most common locations are the floor of the mouth, tongue,

alveolus, palate and upper lip. It has a strong male predilection, and the mean patient age is older than 60 years.[33]

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.[4] The disease is related to smoking and alcohol use.[10]

Histologically, the tumor demonstrates biphasic components of adenocarcinoma and SCC, with an undifferentiated cellular component in several tumors. The SCC 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 be tubular, alveolar and/or glandular.[4][5] Areas of intracellular and intraluminal mucinous material and some acantholytic cells were also seen in lumen of ducts. The amorphous mucinous material within the lumen of ducts was highlighted with periodic acid-Schiff (PAS) and mucicarmine stain.[35] Areas of mucous cells were dispersed within the stroma.[35], although mucus-cell differentiation is not essential for the diagnosis. The cells in the adenocarcinoma can be basaloid and separation from basaloid SCC can at times be arbitrary. The two carcinomas may be separate or intermixed, with areas of commingling and/or transition of the SCC to adenocarcinoma. The 'undifferentiated' areas between the two distinct carcinomas are often composed of clear cells**.** Necrosis, mitotic figures, and perineural invasion are common. There is typically a sparse inflammatory cell infiltrate at the tumor-stromal interface.[4][5]

Differential diagnosis for ASC includes mucoepidermoid carcinoma, adenoid SCC, basaloid SCC, conventional SCC and necrotizing sialometaplasia.[33] ASC is an aggressive tumor characterized by local recurrences, early lymph node metastasis and distant disseminations after treatment. The treatment of choice for ASC has not yet been standardized, but it seems a consensus that the best treatment option should be surgical resection with an adequate safety margin. Additional post-operative therapies, such as radiotherapy and chemotherapy, are not yet consensus on the handling of this clinical entity.[34]

Other Histologic Variants of Squamous Cell Carcinoma

It includes rare variants of OSCC, exophytic or papillary SCC and carcinoma cuniculatum.[1][5][16] Due to the small number of reported cases of these histologic subtypes in the oral cavity, information about their prognosis and clinical–biological behavior has not been established

Conclusion

Clinical as well as histopathological knowledge of any lesion is important to consider the correct diagnosis. Although SCC being the most common malignant neoplasm of the oral cavity, its histologic variants may pose a diagnostic challenge, moreover its clinical and biological course have not been completely established, probably due to the low frequency of these subtypes in the oral cavity. Many histologic variants of SCC are misdiagnosed, either because of lack of adequate representative biopsy sample or may be because of the difficulty in establishing a histopathological diagnosis with routine hematoxylin-eosin staining. Therefore, good sampling and multiple sections should be obtained from various areas of the lesion to ensure correct diagnosis of these variants. The prognosis, metastatic potential, survival rate and treatment of each of these variants are diverse, thus mandating their distinction.

Both clinical and microscopic features of the various histologic variants of OSCC are described in detail in an

attempt to allow pathologists to separate these variants in order to achieve more accurate treatment protocols.

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