Review Article

DOI: 10.17354/ijss/2015/282

Verrucous Carcinoma of the Oral Cavity: Current Concepts

Ankur Kaur Shergill[1], Monica Charlotte Solomon[2], Sunitha Carnelio[3], Abhay Taranath Kamath[4], Chithra Aramanadka[5], Gurshinderpal Singh Shergill[6]

[1]Assistant Professor, Department of Oral Pathology and Microbiology, Manipal College of Dental Sciences, Manipal University, Manipal, Karnataka, India, [2]Professor and Head, Department of Oral Pathology and Microbiology, Manipal College of Dental Sciences, Manipal University, Manipal, Karnataka, India, [3]Professor, Department of Oral Pathology and Microbiology, Manipal College of Dental Sciences, Manipal University, Manipal, Karnataka, India, [4]Professor and Head, Department of Oral and Maxillofacial Surgery, Manipal College of Dental Sciences, Manipal University, Manipal, Karnataka, India, [5]Assistant Professor, Department of Oral and Maxillofacial Surgery, Manipal College of Dental Sciences, Manipal University, Manipal, [6]Assistant Professor, Department of ENT and Head and Neck Surgery, Kasturba Medical College, Manipal, Karnataka, India

Abstract

Oral verrucous carcinoma (VC) is a rare locally invasive tumor. The histopathological diagnosis of verrucous carcinoma should be accompanied with careful identification of tumors with a greater chance to become frank cancers. A comprehensive Google and PubMed search was carried out using "oral, verrucous carcinoma and immunohistochemistry" as the key searching terms. All the articles till date were precisely reviewed and the article was judiciously compiled. It was observed that numerous histopathological, immunohistochemical and genetic studies have been carried on VCs to identify the basis for their non-carcinomatous nature and difference from oral squamous cell carcinomas. The present review elaborates the current concepts of oral VCs regarding the etiology, clinical and histopathological, immunohistochemical and genetic characteristics.

Key words: Carcinoma, Genes, Immunohistochemistry, Verrucous

INTRODUCTION

Verrucous carcinoma (VC) is a rare oral tumor that is classified under carcinomas owing to characteristics that exists amid a benign verrucous lesion and malignant squamous cell carcinoma (SCC). It is a slow growing tumor, which presents predominantly as an exophytic growth with a pebbly, micronodular surface and tends to spread locally with no evidence of metastasis even in advanced cases. A precise diagnosis of VC histopathologically should be accompanied with a careful discrimination between the VCs with a fair and poor prognosis. The article carefully reviews the clinicopathological and immunohistochemical characteristics of VC carefully analyzing the tumors with poor prognosis.

Access this article online

IJSS

www.ijss-sn.com

Month of Submission : 04-2015
Month of Peer Review : 05-2015
Month of Acceptance : 05-2015
Month of Publishing : 06-2015

ORAL VC

Oral VC is an uncommon tumor which presents as a tan/white, warty growth with a broad base attachment.[1] The most common sites for its occurrence include buccal mucosa, mandibular alveolar crest, gingiva, tongue with glottic larynx being the most frequent non-oral site.[2] The tumor rarely crosses 10 cm in its greatest dimension. Literature depicts that VC mostly occurs in males in 5-6th decade of life.[3] Use of tobacco in the smokeless and inhaled forms has been predominantly reported in the affected patients, followed by betel nut chewing and use of alcohol.[4] The oral hygiene is invariably poor in all the cases. The role of human papillomavirus (HPV) in VC has been a matter of debate.[2] The most common differential diagnoses encountered clinically include a spectrum of closely resembling lesions comprising of verrucous hyperplasia, proliferative verrucous leukoplakia and SCC. VC is a locally invading tumor and does not spread to the local lymph nodes. If lymph nodes are palpable, they usually present as an inflammatory reaction in large secondarily infected lesions.[4] When confronted with bony structures such as the mandible, the tumor tends to destroy the bony tissue on

Corresponding Author: Dr. Gurshinderpal Singh Shergill, Department of ENT and Head and Neck Surgery, Kasturba Medical College, Manipal University, Manipal, Karnataka, India. Phone: +91-7483251093. E-mail: shergill243@gmail.com

a broad front, and erodes with a sharp margin rather than infiltrating into the marrow spaces.[5] While surgery forms the widely accepted mode of treatment for VC, radiation is only employed in advanced cases due to reports of radiation induced anaplastic formation in literature.[6]

HISTOPATHOLOGICAL CHARACTERISTICS

VC usually present with a hyperplastic epithelium with abundant keratin superficially projecting as exophytic church-spire keratosis and also depicting parakeratin plugging, which is believed to be characteristic of this tumor. The bulbous well oriented rete ridges show endophytic growth pattern with pushing borders.[7] Abrupt transition from normal epithelium to endophytic ingrowth is taken as an important parameter to differentiate it from benign verrucous growths.[8] The epithelium is well differentiated in all the rete pegs. A classic case of VC shows minimal or no pleomorphism of cells and no mitotic activity above the basal and suprabasal layers of the epithelium.[7] If focal atypia or dysplasia is evident, it must be limited to the basal layer of epithelium. Lymphoplasmacytic inflammatory host reaction is marked, especially in cases where keratin has plunged deep into the connective tissue inducing foreign body granuloma formation.[1] Inadequate biopsy and tangential sectioning often deviate the diagnosis. Insufficient depth of the section, the absence of adjacent normal epithelium, presence of dysplastic features and evidence of micro invasion creates a dilemma for the pathologist and the surgeon and in such cases repeating the biopsy becomes mandatory. In cases with a long tobacco habit history, non-tender or fixed locoregional lymph nodes and bland histopathological picture, it becomes mandatory to rule out SCC.

HYBRID CARCINOMAS

"Hybrid verrucous-squamous carcinoma" term has seldom been used in the literature with most of the cases relating to the transformation of the VC to frank SCC post radiation treatment. The ionizing therapy has been attributed to the above transformation.[6] However, the above hypothesis is not very well supported by current literature where Fonts *et al.* (2006) in his case series reported that 6 of the 10 tumors were, in fact, SCCs and not VCs.[9] Medina *et al.* (1984) reported a coexistence of less differentiated foci of SCCs in VC and supported surgery as the preferred mode of treatment and the use of radiation to be restricted to only selected cases. It has been proved that 20% of the cases of VCs have small foci of well-differentiated SCCs within them and such tumors should be correctly recognized.[10] A correct biopsy with sufficient depth can lead to the precise differentiation between the comparatively better VCs and those with frank malignant foci. Evaluation of the epithelial-connective tissue interface is also a must to precisely rule out SCC foci.

IMMUNOHISTOCHEMICAL SIGNATURE OF VC

VC exhibiting mild dysplastic features or SCC foci need to be carefully examined to rule out frank SCC in the connective tissue stroma. A complete histopathologic examination of an adequate biopsy is augmented with an immunohistochemical evaluation to be completely assured of the diagnosis. A variety of markers has been experimented and identified in VC in comparison with SCC and its benign counterparts.

BASEMENT MEMBRANE CHARACTERISTICS

VC is known to be benign histologically with a locally invasive clinical course. The endophytic growth that is a hallmark of this tumor is due to its resilient basement membrane that probably acts as an effective barrier to prevent the carcinomatous growth. Prioleau *et al.* (1980) in their study on VC of rectum, plantar surface of the foot and oral cavity found marked focal thickening in certain areas of basement membranes and absence in other parts by immunofluorescent examination of anti-basement membrane antibody. They also reported that ultra-structural examination of the tumors revealed reduplicated as well as the normal basal lamina. A proliferative basal zone underlying a thick layer of well differentiated non-proliferating keratinocytes and reduplicated basal lamina were seen in all VCs, regardless of their location.[11] These findings emphasized that basement membrane could play an important role in determining the nature of VC. Jiang *et al.* (2001) detected that oral VC cases showed a thicker basement membrane with reduplication at abundant places and a noticeably greater inflammatory cell infiltration equated to the oral SCC (OSCC) and dysplasia cases.[12]

HPV

The role of HPV in VCs has been a matter of debate since the last few decades. Brandsma *et al.* (1986) analyzed tissue specimens of VC (larynx) by using Southern and DNA dot blot hybridization for HPV DNA. They demonstrated a strong correlation between HPV-16 related sequences and VC of the larynx.[13] Fujita *et al.* (2008) found an inverse co-relation between p53 expression and HPV infection. The development of oral VCs may involve the inactivation of p53, which in turn is associated with HPV infection.[14] Samman *et al.* (2014) utilized next generation sequencing

to investigate the correlation between oral VCs and HPV and found it to be highly insignificant.[15] Lin *et al.* (2010) evaluated p53, murine double minute 2, p21, heat shock protein 70 and HPV 16/18 E6 proteins in 48 VCs and 30 oral verrucous hyperplasia samples. The expression of the above biomarkers was overlapping, and no statistical significant results could be arrived at.[16] Various studies have been done thereafter to correlate HPV and oral VCs, but all have been non-contributory.

EPITHELIUM

Itoiz *et al.* (1993) observed little or no expression of 65-67 Kd keratins in SCC and adenocarcinoma while hyperkeratotic lesions such as VC, leukoplakia, and keratoacanthoma, showed enormous variations in the intensity of 65-67 bands and an irregular immunohistochemical staining pattern. Increased amounts of keratin were usually accompanied by an absence of, or decreased expression of 65-67 Kd keratins, thus indicating a change in the polypeptide composition of the keratin layer in pathological conditions of the oral epithelium.[17] Arduino *et al.* (2010) showed the differences in staining pattern in basement membrane zone of SCC, VCs and severe epithelial dysplasias (SED). The staining pattern of laminin was decreased in SCC compared to SED and VC while collagen IV expression was enhanced in VC as compared to the dysplasia cases.[18] Zargaran *et al.* (2011) demonstrated a significant difference in laminin-332 γ2 (Ln-332 γ2) chain expression in well-differentiated OSCCs and VCs describing their varied biological behavior.[19]

TUMOR SUPPRESSOR GENES AND CELL CYCLE REGULATORS

Gimenez *et al.* (1996) described an overexpression of p53 protein in VCs as paralleled to benign lesions. They also reported an overexpression of cyclin D1 but no variations of Rb staining signifying that Rb may be functionally inactivated by overexpression of cyclin D1 or HPV infection in the low-grade lesions.[20] Saito *et al.* (1999) demonstrated in their study that VCs showed a higher average frequency of p16 positive cells and lower frequency of p53 positive cells than SCCs. The differences in p53 might point toward differences in cell proliferation or states of inactivation of p53 in both the tumors. All the VCs in their study revealed markedly more positive pRb cells than SCCs. Functional inactivation of pRB resulting in overexpression of p16 might pose an important link between VCs and HPV. The percentage of p27 cells was higher in VCs while Ki67 expression was much less as compared to SCCs. This demonstrates a difference in proliferative activity of VCs and SCCs.[21]

Drachenberg *et al.* (1997) tested the expression pattern of bcl-2, p53, and Her-2/neu, and in situ end-labeling of DNA to identify apoptosis in VC and SCC cases. Marked differences were recognized in the pattern of expression of oncogenes and the indexes of cell turnover in these two types of tumors. VC exhibited minimal apoptosis in rare keratinizing cells. P53-positive cells and Ki-67 expression were limited to the nuclei of the basal layers; and bcl-2 expression was observed only in the cytoplasm of tumor cells. In contrast, SCC cases presented higher apoptosis rates, whereas p53- and Ki-67 positive nuclei were dispersed throughout the lesion. SCC cases displayed patchy bcl-2 cytoplasmic staining or strong cytoplasmic and nuclear positivity in the less differentiated tumors. Her-2/neu was negative in all VC and SCC cases. The altered levels and arrays of gene expression and cell turnover amid the verrucous and SCC certainly correlate with the diverse biology and prognosis of the latter.[22]

Sakurai *et al.* (2000) showed an increased expression of c-erbB-3 and proliferating cell nuclear antigen overexpression in the development of VC of the oral mucosa.[23] Lessard and Robinson (2001) revealed a variation in expression of ras signal transduction mediators in VCs as compared to SCC. Raf-1 was strongly expressed in the basal portions of the epithelium in VCs while it showed minimal expression in the suprabasilar epithelial layers. Anti-Raf-1 staining was diffuse and patchy throughout the SCC and was comparatively weaker in intensity. ERK-1 and ERK-2 (extracellular signal-regulated kinases) expression was predominantly cytoplasmic and typically negative in the basal layers of the epithelium in the VCs but was positive in the suprabasilar epithelial layers. ERK-1 and ERK-2 were observed to be diffusely expressed in all the SCC cases.[24]

Wu *et al.* (2002) revealed a lack of noteworthy difference in TGF-α expression in VCs and SCC lesions, but EGFR and p53 expression was greater in OSCCs as compared to the VCs.[25] Chen *et al.* (2002) demonstrated that differential staining of inducible nitric oxide synthase could serve as a predictive marker to differentiate VCs from benign counterparts.[26] Tang *et al.* (2003) demonstrated an increased expression of E-cadherin in VC cases as compared to the poorly differentiated cancers.[27] Kobayashi *et al.* (2003) reported an increased cytoplasmic expression of moesin (a member of ERM [ezrin/radixin/moesin] family) in OSCC cases. They also witnessed a decreased cell membrane expression in the latter cases as compared with oral epithelial dysplasias and VCs. They also recommended the use of moesin as a screening marker in suspected oral mucosal lesions.[28]

Klieb and Raphael (2007) demonstrated a higher frequency of matrix metalloproteinase-1 in adjacent stromal cells

in oral VCs as compared to oral verrucous hyperplasia cases while Impola *et al.* (2004) demonstrated an absence of epithelial matrix metalloproteinases (MMPs) (3, 7, 9, 12 and 13) expression in all VC cases as compared to SCCs establishing their non-invasive behavior.[29,30] Adegboyega *et al.* (2005) reported coinciding patterns of p21 expression in both OSCCs and oral VCs.[31] Ogawa *et al.* (2005) demonstrated that CD44 variant 9 positive oral VCs were linked with lower risk of cervical lymph node metastasis.[32] Ray *et al.* (2011) demonstrated a weak basal expression of VEGF in VCs compared to SCCs. Also, MMP-2 and 9 expression was also very mild as compared to the SCC counterparts demonstrating a non-carcinomatous nature of VCs.[3] Angadi *et al.* (2007) found that cyclin D1 expression and staining pattern was similar in OSCCs and VCs.[33] Laxmidevi *et al.* (2010) studied the β catenin expression in different grades of OSCCs and VCs and reported predominant membranous expression in VCs, which was comparable with well differentiated SCCs. The reduced membranous expression and mainly cytoplasmic localization in poor grade tumors could be linked with loss of cell differentiation and attainment of a malignant phenotype.[34]

Terada (2012) demonstrated a higher Ki-67 labeling index in SCC (64%) as compared to VC (12%).[35] Zargaran *et al.* (2012) in their comparative study between well differentiated SCC and VCs did not find any significant difference in Ki67 expression. The stroma associated with invasive carcinoma is associated with loss of CD34+ dendritic cells and gain of alpha smooth muscle actin myofibroblasts.[36] Chaudhary *et al.* (2012) demonstrated a significant increase in myofibroblastic expression (α SMA) from premalignant lesions to VCs and SCC.[37] Majeed *et al.* (2014) demonstrated a lack of expression of α- smooth muscle actin (myofibroblasts) in oral VC cases as compared to complete positivity in OSCC cases which they attributed to the lack of inductive effect of genetically altered carcinomatous epithelium in VC cases.[38]

EI-Rouby (2010) investigated tumor associated macrophages (TAMs) to evaluate angiogenesis by using CD68 and microvessel density (CD31) in different grades of OSCCs and VCs. They found that increased TAMs were associated with higher grades of cancer as compared to VCs.[39] Quan *et al.* (2012) noted an increase in expression of αB crystallin along with decrease in expression of activated caspase-3 postulating the role of αB-crystallin in anti-apoptosis by inhibiting the activation of caspase-3 in oral VC.[40] Habiba *et al.* (2014) illustrated that the high expression of HuR (ARE mRNA-binding protein) along with a diffuse staining pattern in the epithelium may help in defining the malignant transformation in oral verrucous borderline lesions.[41]

Genetic Studies

Loss of heterozygosity (LOH) studies comparing VCs with different grades of conventional SCCs revealed that VCs had an LOH incidence similar to the well differentiated SCCs as compared to the less differentiated counterparts. VCs were found to possess deletions at 9p and loss of LOH at 4q and 17p, which could contribute to the development of malignancy in the upper aerodigestive region.[42] Gene profiling studies to differentiate oral VCs and SCC showed differences at the level of certain genes, including ADAM metallopeptidase with thrombospondin Type 1 motif, 12 (human) (ADAMTS12), collagen, Type IV, alpha 1 (COL4A1), Collagen, Type IV, alpha 2 (COL4A2), inhibin, beta A (INHBA), MMP-1, plasminogen activator inhibitor-1 (SERPINE1) transforming growth factor, beta-induced (TGFBI) and hepatic leukemia factor (HLF), but the precise genetic abnormalities that could possibly contribute to development of frank carcinoma and the absence of metastasizing potential in VCs still requires more research.[43]

CONCLUSION

VCs present a rare group of lesions in the oral cavity. The presence of malignant foci has been reported in oral VC cases. Consequently, it becomes mandatory for the pathologists to identify VCs, which have greater chance to turn into frank malignancy or with greater chances of recurrence to assist the surgeons in providing a better treatment.

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How to cite this article: Shergill AK, Solomon MC, Carnelio S, Kamath AT, Aramanadka C, Shergill GS. Verrucous Carcinoma of the Oral Cavity: Current Concepts. Int J Sci Stud 2015;3(3):114-118.

Source of Support: Nil, **Conflict of Interest:** None declared.