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VERRUCOUS CARCINOMA, HYBRID VERRUCOUS CARCINOMA & HPV INFECTION: A RETROSPECTIVE RE-EVAUATION & ANALYSIS

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ABSTRACT

Oral Verrucous carcinoma(OVC), is a lesion that was first described by Ackerman & its characteristics include: slow and local growth, invasive nature and rarity of metastases even in advanced cases. Its clinical behavior of invasion, proliferation and exophytic exuberance of epithelial tissue are quite unique to the lesion and thus, has features reflective of both a benign verrucous lesion and an oral squamous cell carcinoma. The common variants of verrucous carcinoma are Oral verrucous carcinoma and Hybrid verrucous carcinoma. The primary purpose of this retrospective study was to investigate the clinical distribution pattern by sex, age, habit and site of Verrucous carcinoma in Chhattisgarh in the last decade and correlate them with the habits and habit duration alongwith histopathological parameters like Dysplasia and its degree, lymphocytic infiltration and nuclear changes indicating HPV infection. The archieves of histopathologically diagnosed Oral Verrucous carcinoma were re-evaluated to delineate Verrucous Carcinomas from Hybrid verrucous carcinomas with their clinical data, habit history and lesion History. On re-evaluation of the histopathological slides from archives it was noted that approximately half the lesions were histologically Hybrid verrucous carcinoma & HPV infection related microscopic changes were evident in histology of both types indicating its minimal role in defining the histological variant. The re-evaluation was an attempt to stress the fact that due to high similarity in staging and grading, it is very important to diagnose and differentiate

Oral hybrid VC from OVC owing to the various common factors that influence their behavior variably and more importantly, due to a distinct difference in their prognosis.

KEYWORDS: Oral verrucous carcinoma, Hybrid verrucous carcinoma, Human Papilloma virus, Koilocytes.

INTRODUCTION

Oral Verrucous carcinoma(OVC), is a lesion that was first described by Ackerman and is also known by various other names in the literature including, Ackerman's tumor, Buschke-Loewenstein tumor, florid oral papillomatosis, epithelioma cuniculatum, and carcinoma cuniculatum. The tumor characteristics include: slow and local growth, invasive nature and rarity of metastases even in advanced cases. Its clinical behavior of invasion, proliferation and exophytic exuberance of epithelial tissue might induce destruction of adjacent tissue like cartilage and bone. Clinically, it presents as a symptomless, large, white patch of an exuberant exophytic growth and predominantly appears similar to a cobblestone-like, numerous minute modules consisting surface. It often occurs on oral mucosae of the buccal pouch area, followed by the mandibular alveolar crest, gingiva, and dorsal surface of tongue.[1,2]

Oral Verrucous carcinoma (OVC) is a carcinoma and has features reflective of both a benign verrucous lesion and an oral squamous cell carcinoma (SCC).

The malignancy usually is only a few centimeters even in its widest dimension. According to researchers Oral verrucous carcinoma is common in males and is seen most often in 5-6th decade of their life.

From among the oral carcinomas the incidence of OVC is between 2% and 12% of all oral carcinomas and according to previous researchers, they show a 5-year survival rate of only upto 50%.[1,2,3]

Most OVC patients have a habit history of tobacco in the smokeless and inhaled both, along-with snuff rubbing. Less commonly seen habits which are usually in combination with the already mentioned primary habits are: betel nut chewing, use of alcohol and poor oral hygiene habits. It may also occur as a long term change or high frequency abuse related alteration in a pre-existing oral potentially malignant disorder.

Infection by Human papillomavirus (HPV) has also been implicated in the etiology of OVC but it has not been proven. HPV subtypes 16 and 18 have been identified in up to 40% of oral VC.

OVC has been categorized into three types by Tang et al., according to its clinical manifestations and prognosis, The three types are: exogenic type, cystoid type, and infiltrative type. The exogenic type of OVC, manifests as an exophytic papillary projections containing growth of a with a slow tumor growth. Unlike this type, the other two types of OVC show a rapid growth and manifests as a bean dreg-like white dry keratosis. The cystoids & infiltrative types are also accompanied by a poorer prognosis compared to the exogenic type of OVC.[4]

The most common clinical differential diagnoses of Oral Verrucous carcinoma includes an array of very similargroup of lesions comprising of verrucous hyperplasia, proliferative verrucous leukoplakia, Hybrid verrucous carcinoma and OSCC.

The treatment of choice for these lesions is surgery, as, the use of radiotherapy is contraindicated in OVC owing to reports that radiation induces anaplastic transformation in this lesion, according to previous researches.[2,4]

Histologically, it shows blunt–ended & broad rete ridges in both light and electron microscopy with features of a local invasive pattern. OVC can become extensive by lateral spread. Despite its histologically benign appearance, it may cause substantial destruction by local invasion. The characteristic bulbous rete ridges comprising the pushing margin of the tumor invasion front tend to compress the surrounding structures including bone rather than infiltration. Lymph node involvement is uncommon if present is usually due to reactive hyperplasia secondary to inflammatory reaction seen at the invasive front of the tumor.[5]

Poor oral hygiene and chronic irritation when present also play an etiologic role as a predisposing factor, and not as a primary factor.[5]

The common variants of verrucous carcinoma are Oral verrucous carcinoma and Hybrid verrucous carcinoma. Hybrid verrucous carcinoma, is histologically an admixture of foci of OVC and differently-differentiated OSCC. This type of carcinoma has a more aggressive & invasive nature and it has an incidence rate up to one-fifth from among all diagnosed cases of OVC. Besides, the published literature also indicates that about one-fifth to one-fourth of

initially diagnosed VC tissues actually show Hybrid architecture of epithelial tissue, by virtue of presence of foci of squamous cell carcinoma in the lesional tissue. This is assumed to be a contribution of the likely "anaplastic alterations" in an OVC. Therefore, when there is histologically detectable verrucous carcinoma (VC) co-existing with an oral squamous cell carcinoma(SCC) arising synchronously and from the same maternal field, it is referred to as Hybrid Verrucous carcinoma. Some parts additionally show an endophytic growth with distinctly discernible broad and proliferative epithelial-connective tissue interface alongwith a moderate lymphoplasmocytic inflammatory host reaction in the juxtaepithelial connective tissue. Inspite of, a high proliferative activity the epithelium of broad rete ridges of the tumor does not show any anaplastic alterations in most areas except, at few, focal & distinct sites where anaplasia is evident and in those areas the tumor exhibits well-demarcated areas of invasion of the juxta-epithelial connective tissue also.[6,7,8]

Hybrid VC is graded and staged similar to SCC .Additionally, within Hybrid VC, the proportion of conventional SCC component & OVC is variable and since, the prognosis of VC is better than SCC hence, it is important to determine the relative proportion of the two co-existing pathologies of OVC & Conventional OSCC. Those lesions with the major proportion of VC would more likely have better prognosis. Unfortunately, very often clinician are not aware of actual quantity of conventional SCC in the given tumor, and only when the pathologist makes an attempt to quantify and specify the proportion of conventional SCC, it becomes possible to determine the treatment protocol variations and also the prognosis.[6]

The general presentation of both lesions is as whitish keratotic growth with occasionally unusual presentation as a mixed red and white lesion. The presence of red component along with white is suggestive of an active inflammatory reaction which could be a fallout of chronic inflammatory reaction due to chronic periodontitis.

The second unusual presentation likely in oral verrucous carcinoma is, the presence of metastatic nodes.

A significant criteria of correct analysis of the histological specimen is a tissue sample of adequate depth in order to allow the precise differentiation between OVC and areas of frank malignant transformation. Thus, thorough scanning of the epithelial-connective tissue interface is very essential to have aclarity on the presence or absence of OSCC niche in the

lesion. The histological evaluation with this context is essential for all clinically labeled Verrucous carcinomas as, the frequency of Hybrid variant in these lesions is not of ignorable proportions.[8,9]

The primary purpose of this retrospective study was to investigate the clinical distribution pattern by sex, age, habit and site of Verrucous carcinoma in Chhattisgarh in the last decade and correlate them with the habits and habit duration alongwith histopathological parameters like Dysplasia and its degree, lymphocytic infiltration and nuclear changes indicating HPV infection.

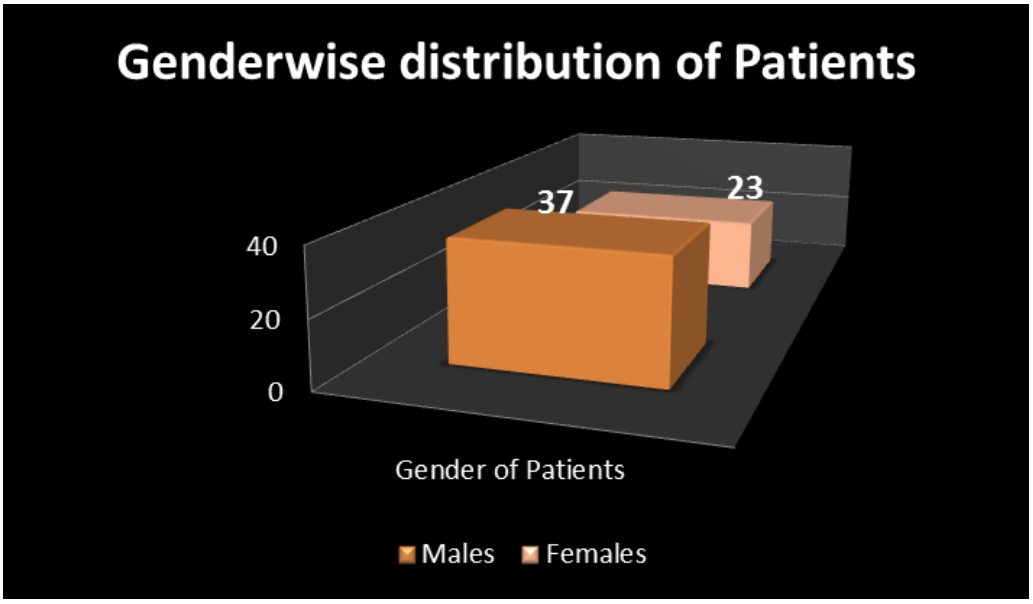
MATERIALS AND METHOD

The archieves of histopathologically diagnosed Oral Verrucous carcinoma of Department of Oral Pathology were re-evaluated to delineate Verrucous Carcinomas from Hybrid verrucous carcinomas. The clinical data of patients was retrieved from the records and tabulated alongwith the details of Habit history and Lesion History.

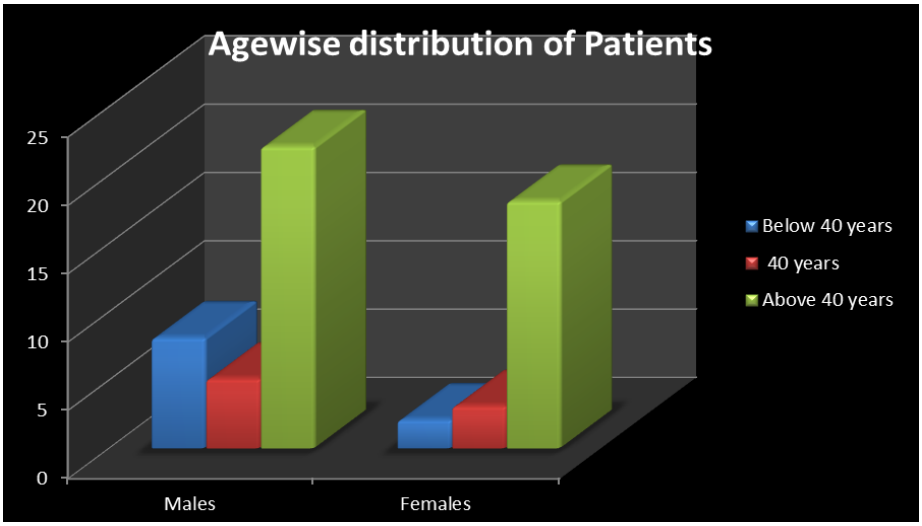
The H & E stained slides of the enlisted patients were re-assessed and observations were analyzed for the type of verrucous carcinoma, degree of dysplasia, degree of lympho-vascular infiltration and the probable Human Papilloma virus infection on the basis of the presence or absence of nuclear pyknosis & perinuclear halo.

DATA ANALYSIS & RESULT

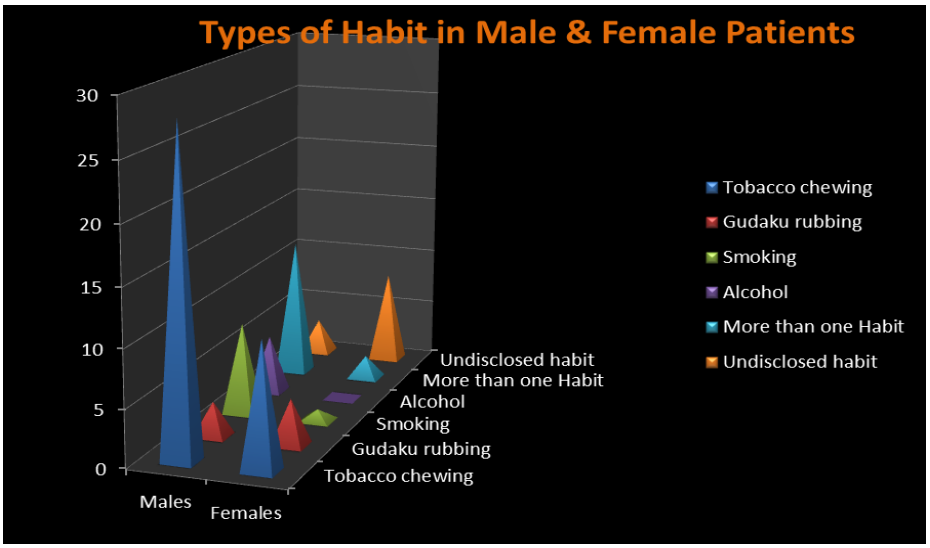
Comparative evaluation of Clinical Data



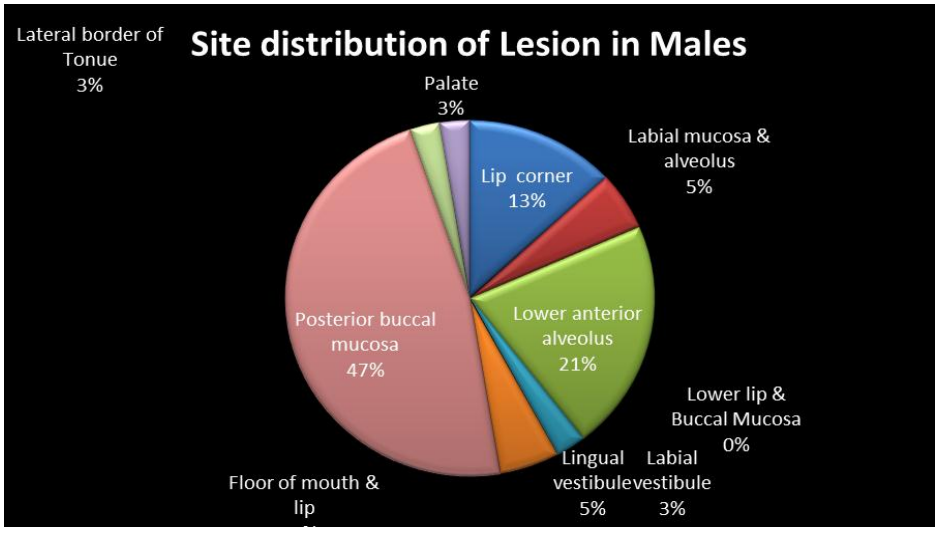
Graph-1CL: Gender distribution of patients.



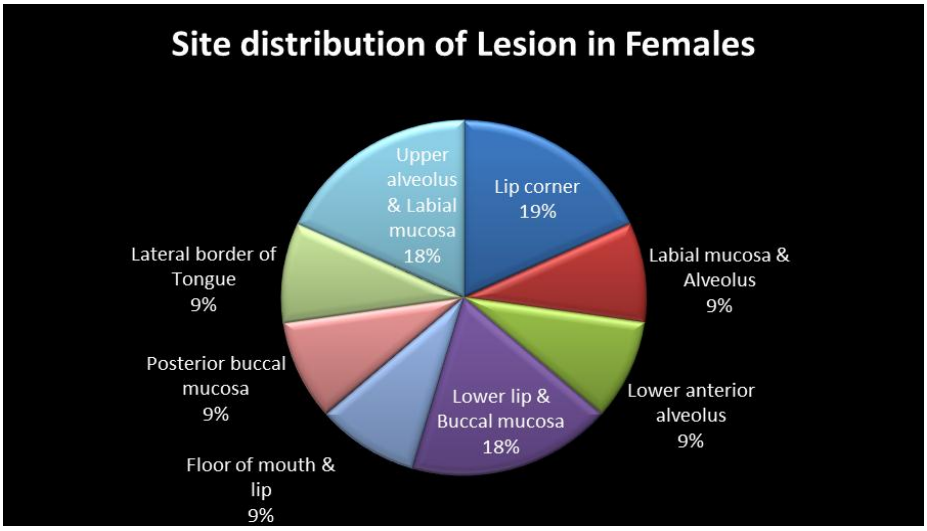
Graph-2CL: Agewise distribution of patients.



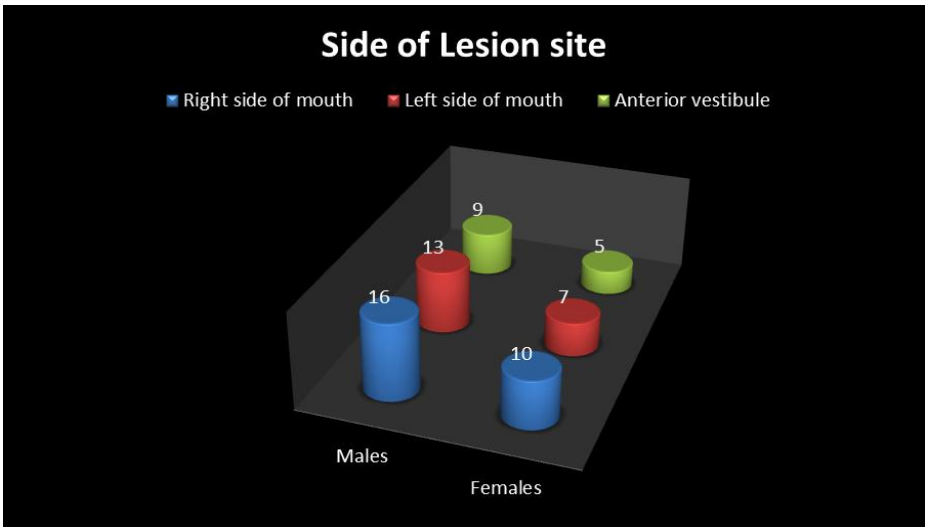
Graph-3CL: Habit correlation in both sexes with lesion occurrence.



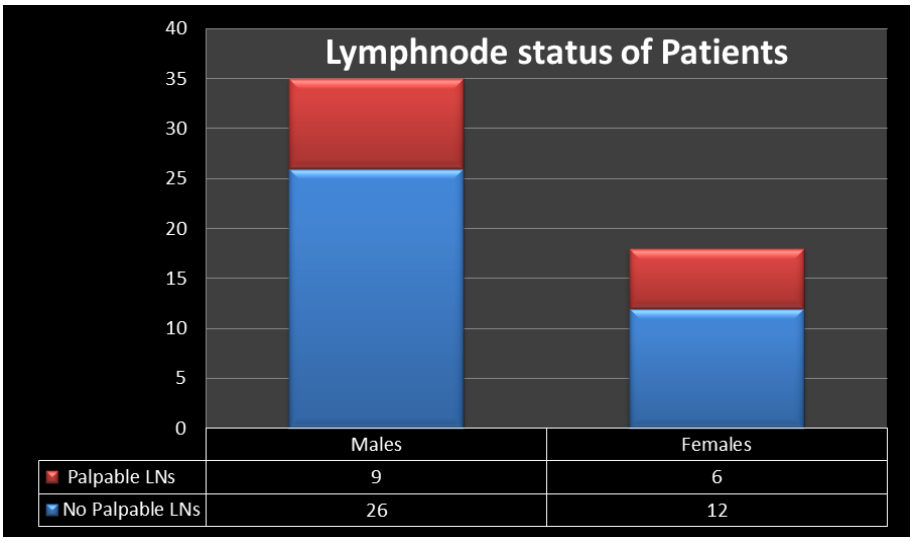
Graph-4CL: Site distribution of lesions in males.



Graph-5CL: Site distribution of lesions in females.



Graph-6CL: Lesion presence side of mouth.



Graph-7CL: Lymphnode status of patients.

Data Analysis of Comparative evaluation of Clinical Data

On evaluation of clinical data the following inferences were drawn

1. Males were more commonly affected than females.(Graph1CL)
2. In both sexes, more patients were in the age group above 40 years, but, in females those of 40 years age were also in significant numbers.(Graph2CL)
3. When habits were correlated with incidence of the carcinoma variants in both sexes(Graph3CL) it was seen that-

a) Tobacco chewing was the most common habit followed by those with more than one habit in males

b) Those with undisclosed habit or gudaku rubbing habit were more in females

4. Majority of lesions were seen in posterior buccal mucosa followed by lower anterior alveolus and corner of lip in males.(Graph4CL)
5. In females, also buccal mucosa, labial mucosa and corner of lip were most frequently involved but lesions were more variable in distribution in females.(Graph5CL)
6. The lesions were more frequent on the right side of mouth followed by left side and then anterior vestibule.(Graph6CL)
7. In both sexes, more number of patients had non-palpable lymph nodes.(Graph7CL)

Thus correlating the clinical findings, it was summarised that, in our observations, the clinical trend of Verrucous carcinoma lesions was more likely to be seen in:
Middle aged males with more than one habit &/or tobacco chewing or gudaku(snuff) rubbing habit. The lesions developed most often in the buccal vestibule and adjacent areas of alveolus, lips or anterior vestibule commonly on the right side of mouth and about 60% of patients did not have palpable lymph nodes.

Comparative evaluation of Histo-pathological Data

Data Analysis

1. The histology of lesions showed that no one type of lesion was predominant but both types were almost similar in their incidence.(Graph1HP)
2. In both histological variants, palpable lymph nodes were observed in equal number of patients.(Graph2HP)
3. When stromal inflammatory response to the epithelial changes was evaluated, the severity of the inflammatory response was more in Hybrid Verrucous carcinoma patients ranging from moderate to severe per microscopic field, whereas, in Verrucous carcinoma the

same was ranging from no inflammation to mild intensity inflammation .(Graph3 & 4 HP)

4. A large majority of both histological types of lesions showed moderate epithelial dysplastic changes to severe changes in a few cases.(Graph 5HP) HPV-induced changes identified as pyknotic nuclei and perinuclear clear halo were noted in each case as present or absent. Presence or absence of dysplasia and its degree were also noted.
5. Epithelial changes suggestive of HPV(Human Papilloma virus) infection like pyknotic nuclei with perinuclear halo were slightly more common in Hybrid Verrucous Carcinoma than in Verrucous Carcinoma indicating probable role of HPV infection in the histo-morphology of the lesion. It thereby, indicated a likelihood of the epithelial alteration due to HPV infection being a probable cause for the Hybrid Verrucous carcinoma more often than Verrucous carcinoma.(Graph 6HP)
6. On analysis of number of patients with HPV infection in both histological types no distinctive indication was obtained as an equivalent number of lesions were found to be of both categories.(Graph 7 HP)
7. On correlation of Epithelial infection, Stromal inflammation and Histology of lesion it was seen that in patients without palpable lymph nodes (Graph 8HP):

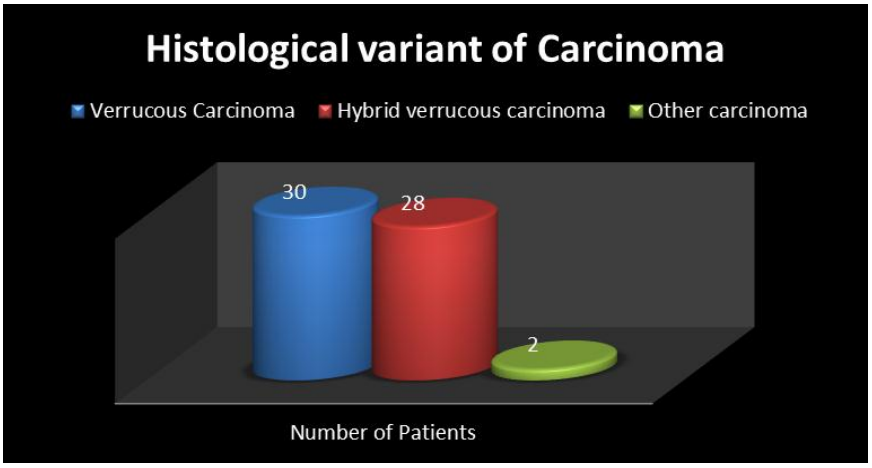
a) From the 14 cases with mild stromal inflammatory reaction 10(6HPV infected[60%]+4 Not infected) were Verrucous carcinoma and 4 were Hybrid Verrucous carcinomas ,all of which were non-infected in the epithelium with HPV. Thus a large majority were Verrucous CA(71%) with about two-third of them showing epithelial infection related changes.

b) In cases with moderate degree of stromal inflammatory response to epithelial changes, reverse was seen ie. 71% cases were Hybrid Verrrucous carcinomas histologically with an equal number of HPV infected and non-infected lesions. Of the 5 cases with Verrucous carcinoma also more (3/5) lesions were having epithelial alterations of HPV infection.

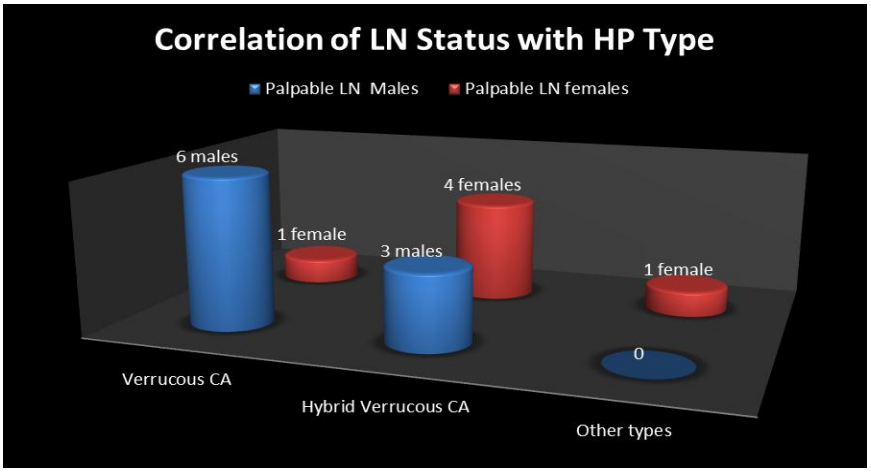
c) In those lesions with an intense or severe stomal inflammatory response to epithelial changes, all the lesions were having Hybrid VC histology and 3 out of 4 lesions showed epithelial alterations indicative of HPV infection.

d) So, these analytical evaluation confirmed that with presence of HPV infection, irrespective of the histological type of oral carcinoma, the stromal inflammatory response was more pronounced.

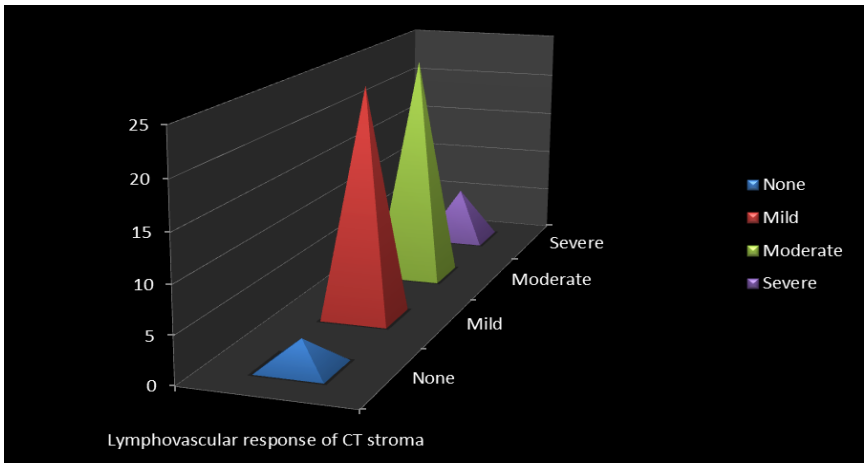
8. In patients with palpable lymph nodes 42.86% showed moderate degree of inflammatory response in the stroma and 52.38% showed mild inflammatory response in connective tissue stroma.(Graph 9HP).



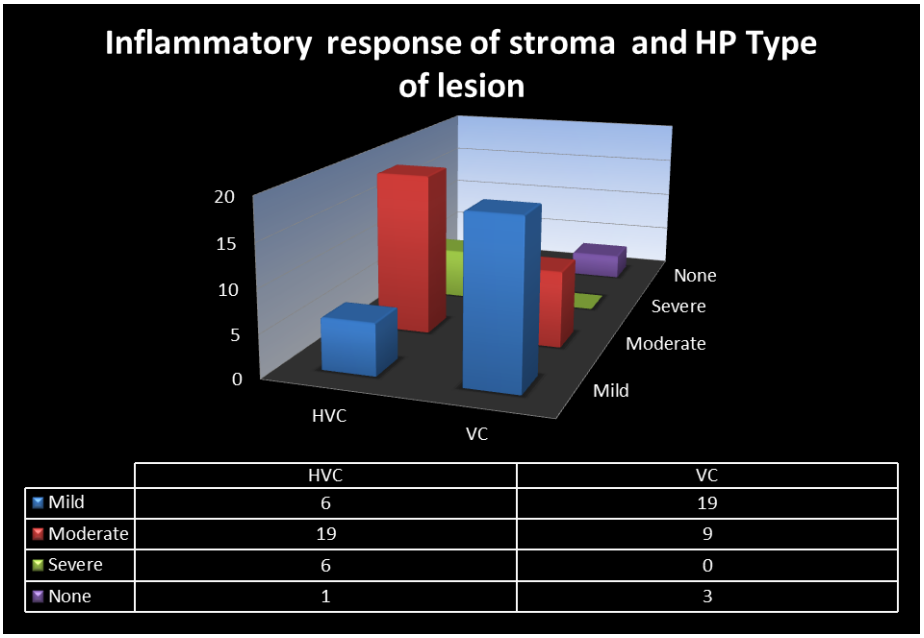
Graph-1HP: Histological type of carcinoma.



Graph-2HP: Correlation of Lymphnode status and histological type.

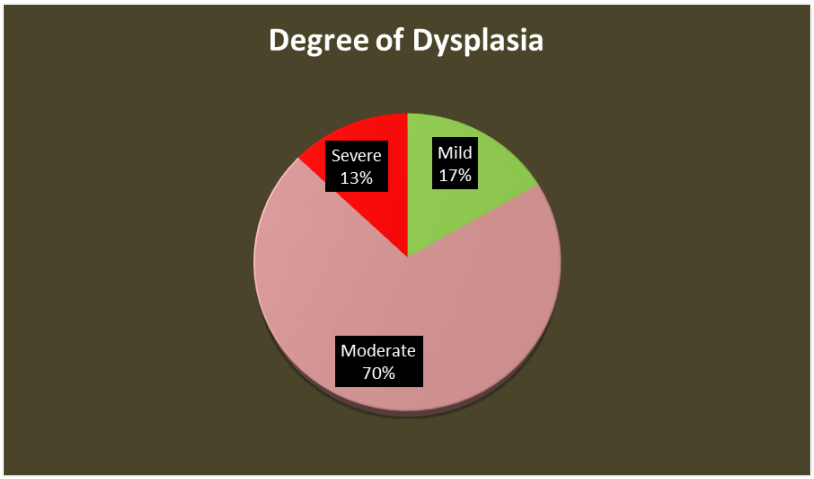


Graph-3HP: Lymphovascular response of stroma.

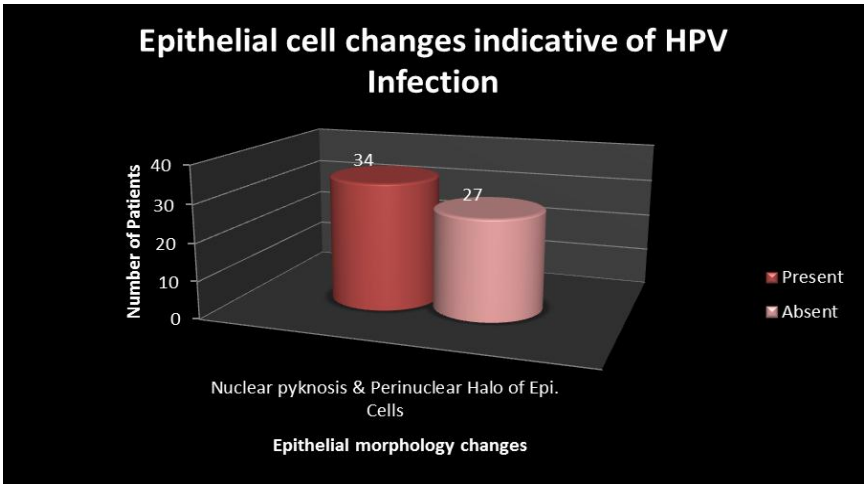


	HVC	VC
Mild	6	19
Moderate	19	9
Severe	6	0
None	1	3

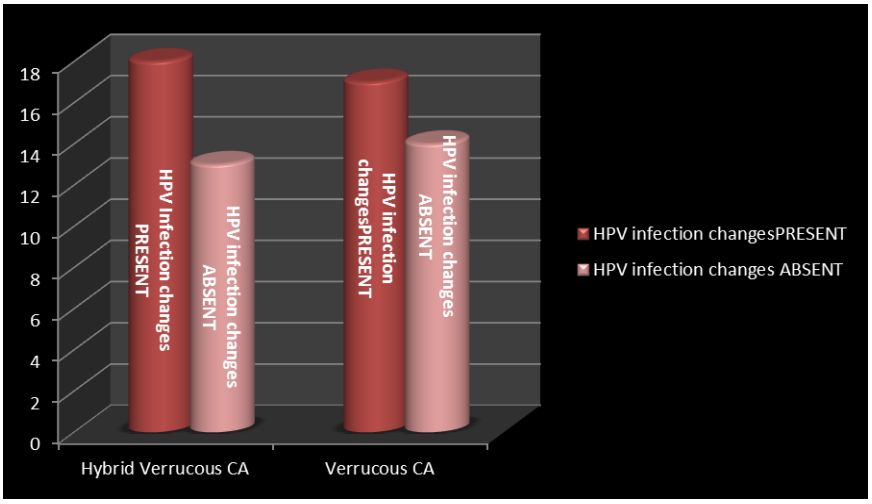
Graph-4HP: Histological type and inflammatory response correlation.



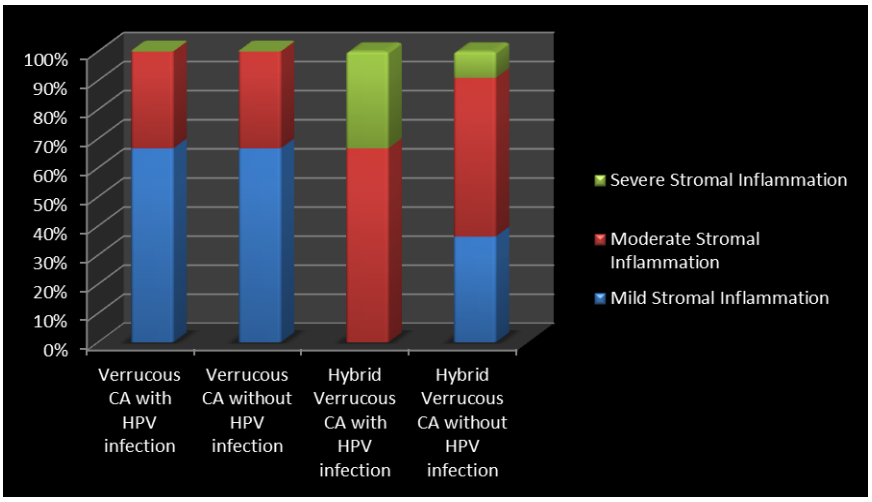
Graph-5HP: Degree of dysplasia among lesions.



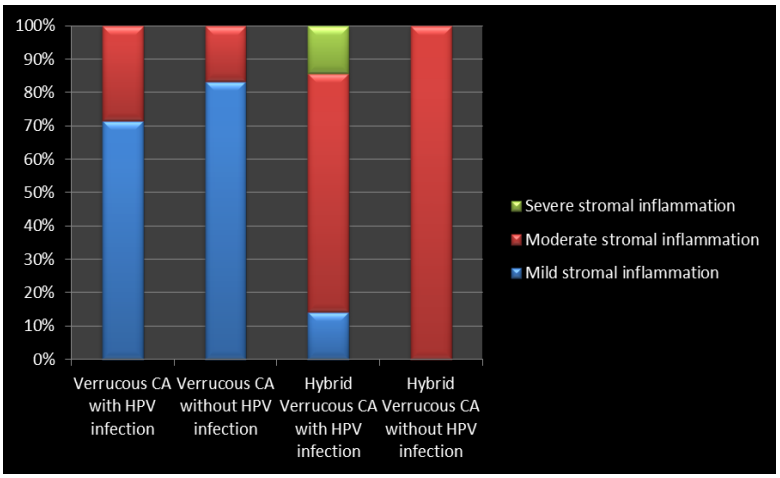
Graph-6HP: Number of lesions with epithelial alterations suggestive of HPV infection.



Graph-7HP: Number of VC & HVC with HPV related epithelial alterations.



Graph-8HP: Correlation of Epithelial infection, Stromal inflammation and Histology of lesion in Patients without palpable Lymph nodes.



Graph-9HP: Correlation of Epithelial infection, Stromal inflammation and Histology of lesion in Patients with palpable Lymph nodes.

(Inflammation intensity 1/α to HPV infection)

In Hybrid Verrucous CA patients with no palpable lymph nodes, it was seen that, with an increase in the intensity of inflammation, the occurence of epithelial alterations indicating HPV infection didn't show a proportional change and only about 56% of total HVC cases had epithelial changes of infection. It, thus, points out that infection of epithelial tissue by HPV doesn't always elicit or correlate with stromal inflammatory reaction and both these are independent of each other. However, in Verrucous carcinoma patients with no palpable lymph nodes, the reverse seemed to be elicited, so that, the HPV infection of epithelial cells was tagged with mild inflammatory response of subjacent connective tissue stroma in a significant number of patients.

In patients with palpable lymph nodes, therefore, the intensity of inflammation seemed to be inversely proportional to the HPV infection status.

DISCUSSION

Incidence

The total number of patients in the 2010-2020 decade of retrospective study were 1859 of which, the number of patients diagnosed with Oral Squamous cell carcinoma/Verrucous carcinoma were 546 (29.37%). From among 546 OSCC patients only 58 patients were of Verrucous carcinoma ie., they represented 10% of the total carcinoma patients (10.623%) and 3.12% of the total patient OPD of Oral Pathology department. This was in accordance with the incidence rate given by other studies for the low-grade, well-differentiated variant of Oral suamous cell carcinoma which represents 2-12% of oral carcinomas.(10) By ratio estimate for 546 total OSCC patients 58 were VC ie. 1:0.10(1:n) or 9.43:1 (n:1). On analysis of the sex ratio men were affected twice as much as the females by VC. The ratio of males to females by **1: n** criteria for OSCC was 1:0.63(1: n) & 1.60:1(n:1) whereas the same for VC was 1:0.49(1:n) or 2.06:1(n:1).s

In this study, the final diagnosis of oral verrucous carcinoma was done on the histopathological characteristics of these lesions. Verrucous carcinoma exhibits a downward growth pattern of otherwise similar rete ridges.[4]

Oral hybrid carcinoma was first described by Jesus E et al, in their study of 104 cases in which the authors reported 20 % of lesions with coexistent less differentiated carcinomas and

also noted that the recurrence of verrucous carcinoma into less differentiated carcinomas was observed in the follow up of these patients.[6]

Etiology

The two proven etiological factors of all oral cancers including OVC are Alcohol and smoking related carcinogens. The etiological role of excessive alcohol consumption in OVC can be explained on the basis of the fact that alcohol may serve as a solvent that enhances the movement of more than 300 carcinogens like, aromatic hydrocarbon benz-pyrene and the tobacco specific nitrosamines (TSNs), present in tobacco smoke or its water-soluble ingredients that will be released into saliva. These products will then enter via oral cellular membranes into cells and thereby, due to persistent consumption will have the capability to change intracellular metabolism of the epithelial cells, leading to deterioration of important cellular functions (e.g., reduced mitochondrial function and enhanced DNA alkylation) in the early phase of oral carcinogenesis. The carcinogens present in areca nut extract give rise to genetic toxicity and teratogenicity in a many types of cells, and thus participate in a vital & substantial manner in in oral carcinogenesis. Additionally, they also lead to DNA single strand breaks and mutations, facilitating tumor formation and growth. A notable role in these carcinogenetic alterations is of Oral microbiota through their significant influence on local metabolism of alcohol and smoking-related carcinogens. Previous researches have highlighted that, five bacterial phyla, including Firmicutes, Proteobacteria, Bacteroidetes, Actinobacteria, and Fusobacteria, are attendant with oral cancer occurence. Theycontribute by activating alcohol and smoking related carcinogens locally.[10]

Most of the severe health effects of smokeless tobacco use come from its chemicals other than Nicotine and according to research by Center for Disease control & Prevention, Smokeless tobacco (SLT) products in the Indian market are likely to have much more nitrosamine content than similar products elsewhere in the world.[11]

The substantial prevalence of smokeless tobacco (SLT) habits in comparison to smoked tobacco in the Indian subcontinent is an undeniable fact which is also noteworthy. Unlike other regions, in South East Asia Region, SLT use among adults is higher than smoking. Among women tobacco users, SLT is the predominant form of tobacco used both due to social taboo and work pressure. The evaluation of carcinogenic risks of smokeless tobacco by the International Agency on Research for Cancer (IARC) has confirmed that SLT is

carcinogenic to humans and the main target organ is their local niche, the oral cavity where the products.[12,13]

The oral effects of smokeless tobacco are typically seen on the mucosal surfaces where the product is placed, as well as on the adjacent periodontium. Clinically, the lesion is usually clearly demarcated from the normal tissues. The affected site or lesion can be a white or yellow-brown colour and it may develop a thickened and wrinkled appearance with increased use of the tobacco product. Smokeless tobacco use in the form of Guddaku(Tobacco+ Molasses), Khaini(Tobacco+ Lime), or Gutka(Tobacco+ Lime+ Arecanut+ Flavoring agents) leads to Oral squamous cell carcinoma & Verrucous carcinoma, as observed by many researchers & highlighted in numerous studies. Also, the development of a carcinoma from smokeless tobacco use is definite but slow — typically, 20 to 50 years of use is required to cause the malignant changes in the oral lesions. The prevalence and severity of lesions demonstrate a dose-response relationship, which is best predicted by the amount, frequency and duration of smokeless tobacco use.[14,15] In our study also, an etiological correlation was observed and so, tobacco chewing was the most common habit followed by multiple habits(Smoked tobacco/Smokeless Tobacco/Alcohol) in males whereas gudaku rubbing habit or undisclosed habit were more frequent observation in females.

Site

It has been observed that the oral cancers due to smokeless tobacco use may occur in sites that are different from the cancers caused by other factors. Users of smokeless tobacco exhibit oral cancer where the quid is held, that is, the buccal or alveolar surfaces. Despite the location, the clinical course of the cancer is similar. The evaluation of carcinogenic risks of smokeless tobacco by the International Agency on Research for Cancer (IARC) based on a large number of epidemiological as well as experimental studies has confirmed that Smokeless Tobacco(SLT) is carcinogenic to human and the main target organ is the oral cavity area where the products are applied locally alongwith its adjacent periodontium.[11] In our study, also majority of lesions were in posterior buccal mucosa or in buccal mucosa & adjacent alveolus &/or corner of lip area in both sexes. Additional observation was greater number of lesions on the right side of oral cavity.

LN status

Verrucous carcinoma has a high potential for local recurrence but not for nodal metastasis & it sometimes appear as multifocal tumor due to field cancerization of the oral cavity by

chronic SLT use. In our study also, majority of patients did not have palpable lymph nodes on presentation.

Clinically, all our cases were diagnosed as OVC due to, a characteristic exophytic mass, cauliflower-like warty lesion and slow growth.

Microscopic features

The microscopic features, showed similarity in both OVC & HVC in terms of HPV infection prevalence and degree of epithelial dysplasia. The number of patients with detectable changes indicating HPV infection in both lesional groups(OVC & HVC) suggest that, the HPV infection is not a governing factor for the type of histological variation but, probably a secondary change due to decreased immune-competency of the patient and microbiology of the local environment of the lesion. The number of patients with epithelial dysplasia and the degree of epithelial dysplasia were similar in both groups but those with mild dysplasia were twice as much in OVC than in HVC.

Also, the HPV infection related epithelial changes were more prevalent in tissue samples of Hybrid verrucous carcinoma patients, giving an affirmative indication of an HPV infection related influence on the epithelial morphology of lesional tissue and hence a more prevalent higher grade of dysplasia in those lesions. This probably also indicates a greater proneness of HVC to super-infection by HPV and a simultaneous more potential of HPV to increase the aggressiveness of infected epithelial cells.

This, would in turn, also explain a more intense and/or likely stromal inflammation in the HVC as compared to OVC.

Hybrid Verrucous Carcinoma(HVC) was defined by Batsakis et al as "A nonverrucous SCC (of varying degree and differentiation) that arises synchronously with the VC and in the same microscopic fields. Hybrid VC is clinically indistinct, but, has a higher tendency for local recurrence. In HVC, the areas of SCC will be the decisive factor for prognostication, hence hybrid tumors are treated as SCC.[5]

On the other hand, as noted by researchers so far, the most important and typical pathological features of OVC are infiltration of all rete pegs into the connective tissue to the same depth thereby forming a pushing epithelial interface. OVC epithelial cells are well differentiated with weak cell atypia. Histologically, the squamous epithelium of OVC shows highly

proliferative, papillary appearance and excess keratosis. The highly proliferative epithelial pegs show swelling and blunt ends in the shape of liquid droplets. These features can be used to diagnose some OVC cases with acceptable accuracy.[10]

However, for accurate diagnosis, multiple factors except for clinical and pathological features should be considered to eliminate the influence of other lesions on discrimination, such as Hybrid VC due to OSCC within OVC. The main reasons of not being able to get gold diagnosis standards of differential diagnosis of OVC from Hybrid verrucous carcinoma is because Hybrid verrucous carcinoma is composed of OVC and differently-differentiated OSCC and this type of carcinoma has more aggressive invasion nature with incidence rate up to 20%. The proportion of conventional OVC component may vary and the prognosis of hybrid VC with high proportion of OVC may have better prognosis than OSCC.[10]

In our study, by re-evaluation of the histopathological slides from archives it was noted that approximately half the lesions were histologically Hybrid verrucous carcinoma & HPV infection related microscopic changes were evident in histology of both types of Verrucous Carcinoma indicating its minimal role in defining the histological variant. The re-evaluation was an attempt to stress the fact that due to high similarity in staging and grading, it is very important to diagnose and differentiate Oral hybrid VC from OVC owing to the various common factors that influence their behavior variably and more importantly, due to a distinct difference in their prognosis.

CONCLUSION

Clinically as well as microscopically, a thorough evaluation of a Verrucous carcinoma is essential to be able to more authentically plan its treatment and predict the prognosis.

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Conflicts of Interest- None.

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