Case Report

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Pathology Section

Verrucous Carcinoma with Oral Submucous Fibrosis: A Rare Case with Brief Review

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ABSTRACT

Oral verrucous carcinoma (VC) is a variant of well differentiated oral squamous cell carcinoma (OSCC) characterized by exophytic over growth. Oral submucous fibrosis (OSMF) is a potentially malignant disorder associated with chronic betel nut chewing habit. The development of OSCC is seen in one-third of the OSMF patients, but the development of VC is rare in such patients. There are very few cases of OSMF with VC reported in literature. Here, present a rare case of an elderly patient with VC in conjunction with OSMF.

Keywords: Fibrosis, Oral squamous cell carcinoma, Proliferative verrucous leukoplakia, Verrucous hyperplasia

CASE REPORT

A 60-year-old male patient reported with a painless, white proliferative growth present on the right labial mucosa for the past 5 months. The patient used to chew 8 to10 packets of gutkha per day for the past 30 yr. Ten years back, he developed burning sensation and difficulty in opening the mouth and thereby stopped chewing gutkha. Recently, five months ago, he developed a growth on the right labial mucosa. Initially the growth was small which increased steadily gradually, expanding laterally and vertically to the present size.

On clinical examination a whitish exophytic growth was seen on the right labial vestibule 0.5 cm below the commissural area, extending posteriorly to the buccal mucosa and onto the adjacent gingival. The lesion was irregular in shape measuring approx 3.5x3cm with a corrugated and papillary surface. The lesion closer to the commissural area was more verrucous and thicker. Tiny isolated lesions were noted on the labial attached gingiva in relation to 42. The lesion was tender on palpation, firm in consistency and indurated [Table/Fig-1a]. The patient's mouth opening was 1.5cm. Blanching and palpable fibrotic bands were present in both involving right and left buccal mucosa. The entire oral mucosa was pale with focal blanched area [Table/Fig-1b]. A clinical diagnosis of VC (for main as well as for tiny lesion) and OSMF was made. As the lesion was indurated differential diagnosis of carcinoma of buccal mucosa was made.

Incisional biopsy was performed under local anesthesia and tissue was sent to histopathological laboratory for microscopic evaluation. Microscopic examination showed parakeratinised stratified squamous epithelium proliferating extensively into the underlying connective tissue. The epithelium showed broad and bulbous rete ridges with pushing margins. Parakeratin plugging extending from the surface into the epithelium was seen [Table/Fig-2a,b]. No dysplastic features were evident. The underlying connective tissue showed dense chronic inflammatory cell infiltration especially in the sub-epithelial region. Another bit of tissue showed atrophic epithelium with loss of rete ridges. Underlying connective tissue was fibrous with dense bundles of collagen fibers with minimal vascularity. Thus on the basis of histopathology final diagnosis of OSMF with VC was given.

Patient underwent cryosurgery with open spray technique used which leads to complete regression of white papillary growth from oral cavity [Table/Fig-3]. Open spray technique emits a fine spray of a cryogen on the target area. The patient was treated for OSMF with intralesional steroids and hyaluronidase injections. Now condition of patient is stable and he is under regular follow-up. The patient's mouth opening has improved and there is no evidence of recurrence of white lesion.

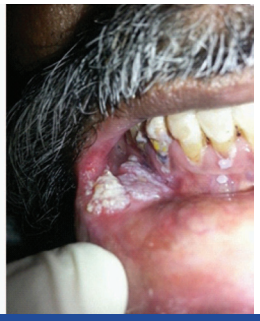
DISCUSSION

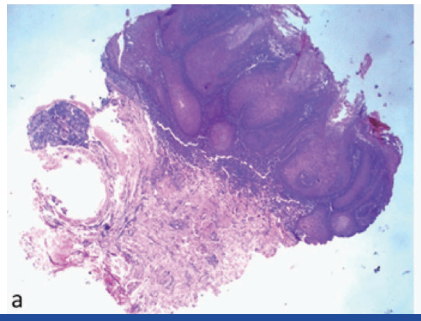
The development of OSCC is generally predicted depending upon the development of multiple, clonal, genetic alterations, which lends a clonal population of cells a growth advantage over the others. Due to the mechanism by which oral mucosa undergoes transformation in OSCC, i.e. chronic exposure to carcinogens in the form of tobacco, betel nut, with alcohol as a cocarcinogen, there are a wide variety of molecular alterations that have been associated with carcinogenesis. In addition to dysregulation of oncogenes and tumour suppressors, cytogenetic changes, epigenetic changes and mitochondrial mutations have been implicated in development of OSCC. These alterations are reflected in varying degrees in potentially malignant disorders [1].

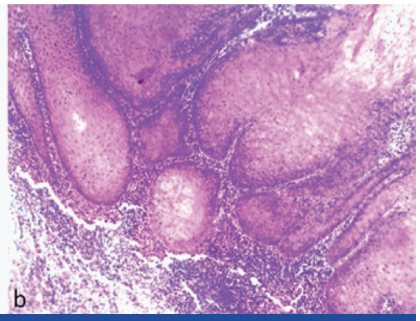
VC was first defined by Ackerman in 1948 as a pathological entity [2]. The etiology of oral VCs is not completely established but it is suggested that risk factors include tobacco both inhaled and smokeless forms [3]. According to Shear and Pindborg tobacco chewing appears to be the major causative factor for VC [1]. It may occur as a consequence of snuff dipping or as an advanced stage of proliferative verrucous leukoplakia (PVL) [4]. Human papilloma virus has been identified in the cells of this tumour but its role is still undetermined [2]. Studies have found that the DNA aneuploidy can be the sustained event in the development of verrucous carcinoma VC [5]. Diagnosis of VCs can be difficult and is normally based on histopathological examination of clinically suspicious oral lesions [5].

Studies have shown cases of OSCCs developing within VC. It is also suggested that VC may arise via dysplasia–carcinoma in situ sequence, and finally transform into invasive squamous cell carcinoma. Cases of VCs often show microinvasion, suggesting that the atypical basal cells of VC underwent invasive characters [6]. The expression of p53 protein and Ki-67 antigen in VC is accentuated in the basal cells and at the invasive sites. The expression of p53 and relatively low Ki-67 labeling supports that VC is a low grade malignant tumour [6]. That is why may be the squamous cell carcinoma arising from VCs is often of well differentiated type. The expression of both these proteins in the basal areas may indicate that the basal part of VC has a relatively higher p53 mutation and cell proliferative capacity than the other parts of VC.

Studies have also found that in VC the expression of laminin and collagen IV in the basement membrane is continuous and regular which is not noted in cases of OSCC [7].

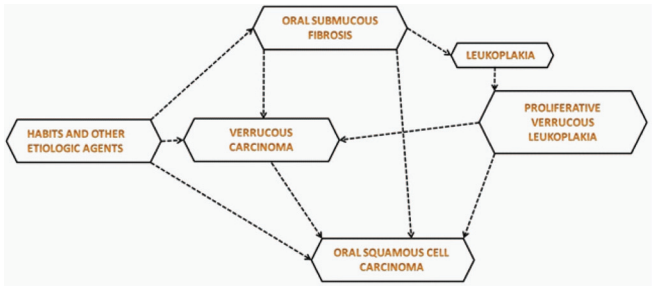




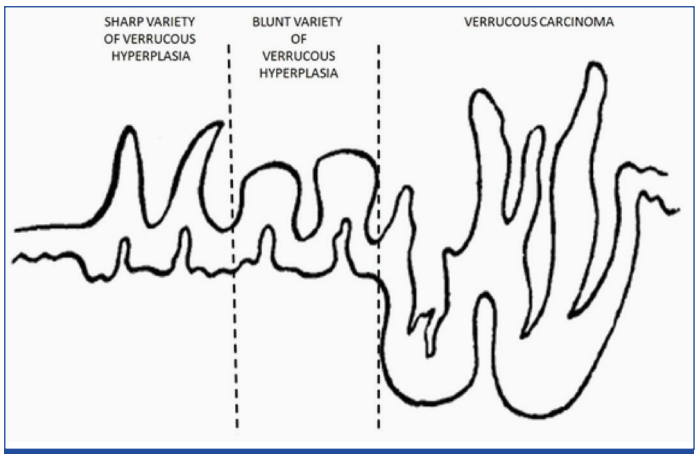


[Table/Fig-1a]: Patient's profile showing limited mouth opening **[Table/Fig-1b]:** White papillary growth involving right labial mucosa and vestibule **[Table/Fig-2a]:** Photomicrograph showing stratified squamous epithelium with parakeratotic plugging (4x magnification) **[Table/Fig-2b]:** The epithelium showing broad and bulbous rete ridges which seemed to push the adjacent connective tissue (40 X magnification)

[Table/Fig-3]: Complete regression of lesion after cryotherapy



[Table/Fig-4]: Illustrating possible role of factors in development of verrucous carcinoma



[Table/Fig-5]: Diagram showing main histological difference between VH and VC

OSMF is a chronic insidious disease characterized by irreversible generalized fibrosis of the oral soft tissues [8]. The disease affects most part of the oral cavity as well as the upper third of the esophagus [9]. OSMF is most often associated with chronic betel nut chewing containing areca nut [8]. The amount of areca nut in betel quid and the frequency and duration of chewing betel quid are clearly related to the development of OSMF. Patients with OSMF develop stiffness of the oral mucosa and a limitation in opening the mouth. In this case the patient who was a gutkha chewer had a mouth opening of only 15mm.

The pathogenesis of OSMF is not well established, although a number of possible mechanisms have been suggested. Pathogenesis is believed to involve juxta-epithelial inflammatory reaction and fibrosis in the oral mucosa, probably due to increased cross-linking of collagen through up-regulation of lysyl oxidase activity. Fibrosis results from the effects of areca nut, which increases collagen production and decreases collagen degradation. The initial pathology of OSMF is characterized by juxta-epithelial inflammation which initially composed of neutrophils and then plasma cells and lymphocytes. In more advanced stages, OSMF is characterized by formation of thick bands of collagen and hyalinization extending into the submucosal tissues and decreased vascularity.

OSMF may cause atrophy in the epithelium, increasing carcinogen penetration. Studies suggest that dysplasia is seen in about 25% of biopsies of OSMF cases and the rate of transformation to malignancy varies from 3% to 19%. The evidence supporting the malignant potential of OSMF includes [8]: (i) higher prevalence of leukoplakia among OSMF patients; (ii) high frequency of epithelial dysplasia; (iii) histologic diagnosis of carcinoma without the clinical signs of carcinoma; (iv) concurrent finding of OSMF among patients with oral cancer; and (v) incidence of oral cancer among patients with OSMF.

Although development of squamous cell carcinoma is seen in one-third of OSMF patients, this occurrence is said to be extremely rare [2]. OSMF a potentially malignant disorder may also give rise to VC [Table/Fig-4]. Alternatively, VC may develop de novo or from an exsisting existing PVL [6] [Table/Fig-4]. Due to very few cases reported in literature a definite conclusion cannot be established as to whether the OSMF in this case has caused the development of VC or if it is just an incidental finding. Also, in the present case, the patient is a gutkha chewer and has no other habits commonly associated with VCs. So, it can be inferred that here OSMF could be the cause for the development of VC.

There are very few cases of VC with OSMF reported in literature. Case of VC with OSMF has been reported in a younger patient with long standing history of chewing tobacco. In this they also stated that VC may arise de novo or it may arise from potentially malignant lesions.

A distinction should be made between VC and other verrucous lesions especially PVL. PVL is an uncommon progressive form of multifocal leukoplakia with high rate of malignant transformation to either OSCC or VC and a high probability of recurrence. Although the lesions typically begin as simple, flat hyperkeratosis that is indistinguishable from ordinary leukoplakic lesions, PVL exhibits persistent growth eventually becoming exophytic and verrucous in growth. Verrucous hyperplasia (VH) is an antecedent or early form of VC and should be treated as VC. VH may develop from leukoplakic lesions [10]. VH is best distinguished from VC in biopsies taken at

the margins of the lesions. In the former, the verrucous processes and greater part of the hyperplastic epithelium are superficial to adjacent normal epithelium [Table/Fig-5]. Whereas in the latter, the verrucous processes are superficial, but the broad rete processes extend considerably deeper than the adjacent normal epithelium, often pulling a margin of normal epithelium down with them into the underlying connective tissue [10].

TREATMENT OPTIONS

Surgery is considered the primary mode of treatment for oral VC [1]. Oral VC has an excellent prognosis with surgical management. Surgical excision and primary grafting with regular long term follow up for recurrence can be considered as a feasible option for treatment of oral VC. The treatment of OSMF has been concentrated on attempts to improve opening of the mouth by medical or surgical means. Surgical excision and skin grafting are applicable where the areas of fibrosis are localized and access is unrestricted [3]. Thus, surgery has not always been attempted in severe and diffuse cases of OSMF. Attempts to improve the opening of the mouth by merely surgically dividing the fibrous bands may make matters worse by increasing scarring [3]. Split thickness skin grafting following bilateral temporalis myotomy or coronoidectomy has been advocated.

CONCLUSION

Verrucous carcinoma may arise de-novo or from preexisting potentially malignant lesions. Here we report the case of VC in association with OSMF which is a rare occurrence.

LIST OF ABBREVIATIONS USED

- Oral verrucous carcinoma (VC)
- Oral squamous cell carcinoma (OSCC)
- Oral submucous fibrosis (OSMF)
- Proliferative verrucous leukoplakia (PVL)
- Verrucous hyperplasia (VH)

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