

# Verrucous Carcinoma

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**Abstract:** *Verrucous carcinoma is a relatively uncommon, locally aggressive, clinically exophytic, low-grade, slow-growing, well-differentiated squamous cell carcinoma minimal metastatic potential. Verrucous carcinoma may involve the oral cavity, larynx, anogenital region, plantar surface of the foot, and, less commonly, other cutaneous sites.*

**Keywords:** Verrucous, Carcinoma, Exophytic

## 1. Introduction

Verrucous carcinoma or Ackermann's tumor is considered a frequently presenting at the oral mucosa and skin. Oral verrucous carcinoma clinically presents as a proliferative or cauliflower-like lesion or as ulceroproliferative lesion on the buccal mucosa followed by other sites such as the gingiva, tongue, and hard palate. [1]

It's more common in tobacco user and more predilection in males. The histopathological diagnosis of verrucous carcinoma is quite difficult and need immense expertise to report a case of verrucous carcinoma. [2]

Though verrucous carcinoma is a benign lesion with minimum aggressive potential however long standing cases shows transformation into squamous cell carcinoma. [3]

Oral Verrucous Carcinoma (OVC), a variant of Squamous Cell carcinoma (SCC), was first described by Lauren V Ackermann in 1948 so it was known as 'Verrucous Carcinoma of Ackermann' or "Ackermann's Tumor".<sup>1</sup> other names used in literature are Buschke-Loewenstein tumor, florid oral papillomatosis, epitheliomacuniculatum, and carcinoma cuniculatum. [4]

Verrucous carcinoma (VC) is a rare variant of well differentiated squamous cell carcinoma.[5]

Oral cancer often manifests itself in about 45%-48% of cases as ulcers or ulcerated tumors. Owing to its wide range of causative factors and unpredictable presenting features, the diagnosis of oral ulcerative lesions might be quite challenging. [6]

In initial cases, these carcinomatous ulcers can be confused with other pathological entities and often misdiagnosed as nonneoplastic ulcerative lesion. Such lesions lasting for two weeks or longer often create a dilemma due to its chronicity and unresponsive behaviour to various treatments prescribed. [7]

### Etiology:

OVC has complex etiology which depends on a variety of factors. [8] There exist strong associations between OVC and alcohol consumption, smoking, areca nut chewing and oral microbiota .[9]

These factors may act individually or synergistically in oral carcinogenesis. OVC also has a relationship with undesirable prosthesis, earlier injuries and scars, and chronic inflammation. Moreover, it may occur as a result of deterioration of premalignant lesions, including oral verrucous leukoplakia, oral lichen planus, oral submucous fibrosis (OSF), odontogenic keratocyst. [10]

Alcohol and smoking related carcinogens are two main well-established risk factors for oral cancers including OVC. [11]

Excessive alcohol consumption can increase incidence of OVC because alcohol may act as a solvent that promotes movement of carcinogens via oral cellular membranes, as the consumption has the capability to change intracellular metabolism of the epithelial cells, causing impairment of cellular function (e.g., reduced mitochondrial function and enhanced DNA alkylation) in the initial phase of oral carcinogenesis. Similar to alcohol consumption, smoking is another potential factor that may induce OVC. [12]

In fact, there exist over 300 carcinogens, i.e., aromatic hydrocarbon benz-pyrene and the tobacco specific nitrosamines (TSNs), in tobacco smoke or its water-soluble components that will leach into saliva. These carcinogens interfere with DNA replication by generating DNA adducts, primarily O<sup>6</sup> methyl Guanine, damaging replicating cells of the immune response . [13]

### Clinical Features:

OVC often occurs in buccal mucosa, tongue, lip, gingiva, alveolar ridge and mouth floor, exhibiting a predilection for elderly males, especially those over the age of sixty.[14]

Its predominant clinical manifestations are exophytic mass and papillary appearance. Due to its slow growth which contributes to long medical history (up to several years) and to the local aggression that leads to rare regional or distant metastasis, OVC has a relatively good prognosis. [15]

According to clinical manifestations and prognosis, Tang et al first divided OVC into three types: exogenic type, cystoid type, and infiltrative type.[16]

The exogenic type of OVC is characterized by exophytic growth, cauliflower-like warty lesion and slow tumor growth. However, the other two types of OVC grow rapidly, forming bean dreg-like white dry keratosis, accompanying poor prognosis compared to the exogenic type of OVC.

**Pathological Features:**

OVC epithelial cells are well differentiated with weak cell atypia. In optical microscopy, the squamous epithelium of OVC shows highly proliferative, papillary appearance and excess aceratosis. The highly proliferative epithelial pegs show swelling and blunt ends in the shape of liquid droplets. All epithelial pegs are infiltrated to the connective tissue in the same depth, forming pushing borders. [17]

Many lymphocytes and plasma cells are also infiltrated into the connective tissue in which cancer cells may degenerate or become necrosis or be swallowed by phagocytic cells, resulting in carcinoma cell destruction. [18]

**Histopathological Features:**

Papillary proliferation and severe thickening of squamous epithelium are observed. Swelling of nuclei and mitoses are found occasionally. The invasion into the basement membrane is not detected. [19]

Papillary proliferation and severe thickening of squamous epithelium are also observed. Single cell keratinization and incomplete pearl formation are found occasionally. The basement membrane is partially disappeared. [20]

Lesions showing a keratotic exophytic surface composed of sharp or blunt epithelial projections with keratin-filled invaginations (plugging), but without obvious fibrovascular cores.[21]

VC, a warty variant of squamous cell carcinoma is characterized by a predominantly exophytic overgrowth of well-differentiated keratinizing epithelium. [22]

Histologically, it is known to present “elephant feet” like downgrowth that seems to compress the underlying connective tissue and typically show minimal or absent cytological atypia.<sup>13</sup> The associated basement membrane appears intact. [23]

In the most advanced stages, bone, salivary glands, muscles and cartilage involvement can be seen. VC should be analyzed regarding.

- a) Conventional SCC, especially with those SCC showing “verruroid” features.
- b) Proliferative verrucous leukoplakia (PVL).
- c) Reactive keratosis and epithelial hyperplasia.
- d) pseudoepitheliomatous hyperplasia.
- e) verruca vulgaris.
- f) keratoacanthoma when verrucous carcinoma affects cutaneous sites and their hybrids. [24]

VC was composed of squamous cell proliferations with verrucous or papillary features .The tumor cells had acidophilic, ample cytoplasm, and the nuclei were round and mildly hyperchromatic.[25]

The cellular atypia was mild or minimal. Individual eratinization), squamous pearl formation, koilocytosis and basal cell mild atypia were recognized. Some microinvasion.

Some had focal ordinary squamous cell carcinoma within the VC .Dysplasia of the surrounding squamous epithelium was found. Lymphocytic infiltration in the dermis was recognized. [26]

**Differential Diagnosis:**

Although much effort has been spent on differential diagnosis of OVC, gold diagnosis standards or specific diagnostic markers are still lacking. The main reasons are as follows: First, OVC is similar to many diseases in clinical and pathological aspects. Different OVC cases may show different biological behaviors. Second, for the same OVC, it may be diagnosed differently when pathological examination is performed on different sites. Third, hybrid verrucous carcinoma, composed of OVC and differently-differentiated OSCC, may exist. This type of carcinoma has more aggressive invasion nature with incidence rate up to 20% (76). Obviously, it is crucial to make a differential diagnosis between OVC and other similar diseases for improving treatment and prognosis. [27]

**Treatment**

Surgery was the most reliable treatment method for OVC; however, radiotherapy combined with chemotherapy was the next most preferable treatment when surgery was not undertaken. We also found that highly malignant transformation (anaplastic transformation) occasionally occurred during treatments for OVC.[28]

Verrucous carcinomas are considered to have poor radioresponsiveness and radiotherapy has been reported to induce anaplastic transformation. Surgery has been considered to be the primary mode of treatment for these tumours.[29]

The patients who undergo surgery are usually in Stage I or II, whereas radiotherapy (or combined with surgery) appears more suitable for patients in Stage III or IV, the advanced tumor stages which are not an indication for surgery. [30]

It was shown that the 5-year actuarial survival of patients with OVC treated by primary radiotherapy did not show any significant difference when compared to that of patients treated by surgery.[31]

In this regard, the role of radiation in promoting anaplastic transformation, a risk which is certainly over-emphasized, seems questionable and warrants further verification shows representative satisfactory results obtained by using radiotherapy for OVC treatment. Overall, radiotherapy was deemed less effective but an acceptable alternative treatment regimen for OVC. [32]

Surgery and radiation are the major treatments for the exogenic type of OVC. However, for some OVC with strong tendency to local invasion, chemotherapy may be another cost-effective alternative treatment for patients, which usually improves the quality of life considerably. [33]

For instance, intra-arterial chemotherapy, featured by convenient dosing, excellent drug activity and acceptable

toxicity profile, is effective in some OVC patients. Chemotherapeutic drugs have the capacity to evoke rapid and clinically significant sustained response which can be well tolerated in the patients. [34]

Carbon dioxide (CO<sub>2</sub>) laser therapy has been introduced to treat patients having oral lesions. The advantages of this treatment include short surgical time, effective wound sterilization, fast hemostasis and healing process, little pain, sealing of adjacent lymphatic vessels, reduced spread of malignant cells and anti-metastasis. [35]

## 2. Discussions

Verrucous carcinoma (VC) is an exophytic, warty, and cauliflower-like tumor and a slowly growing, well-differentiated variant of squamous cell carcinoma. VC rarely metastasizes to lymph nodes and distant organs. It is found most commonly in the oropharynx, genitalia, and the soles of the feet. VC of the esophagus is very rare and difficult in preoperative diagnosis. The patients ranged in age from 36 to 78 years old (median = 63). Males predominated (23 cases versus 13, with the gender in 2 unknown). The most common chief complaint was dysphagia, in 30 out of the 38 cases (79%). The tumor was located in the upper esophagus in 9 cases, the mid-esophagus in 7 cases, and in the lower esophagus in 20 cases. In two cases, the tumor involved the entire esophagus. [36]

OVC has received increasing attention in the past decades, which has been demonstrated by much effort spent on its etiology, clinical manifestations, pathology, diagnosis and treatment. There were evident advancements in this field, covering from etiological analysis to effective treatment.

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