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Oral Florid Papillomatosis

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Introduction

Background

Oral florid papillomatosis is a type of verrucous carcinoma (VC) that is clinically evident as multiple squamous papillary nodules in the oral cavity and, less commonly, in the larynx, the pharynx, the esophagus, the middle ear, the maxillary antrum, the nasal fossa, and the bronchus. Verrucous carcinoma usually appears in 3 main sites: the oropharynx, the genital tract, and the soles of the feet. However, verrucous carcinoma can also occur on the cutaneous surface. Accordingly, verrucous carcinoma is known by a number of names.

Oral florid papillomatosis is best defined as a type of verrucous carcinoma, although some consider it a separate entity. Still others consider it a disease on a continuum between viral warts and verrucous carcinoma, rather than a verrucous carcinoma per se.[1] Lauren V. Ackerman[2] described oral verrucous carcinoma and coined the term verrucous carcinoma. Oral, laryngeal, pharyngeal, and esophageal lesions of this type are generally known as a verrucous carcinoma or an Ackerman tumor.

Although the term verrucous carcinoma followed by its anatomical site would be the most comprehensive name, the historical name justifiably favors honoring 2 eminent physicians, Abraham Buschke (1868-1943) of Berlin and Ackerman (1905-1993). Buschke was a legendary professor of dermatology, and Ackerman, the renowned professor of pathology, developed the concept of verrucous carcinoma. However, the descriptive name oral florid papillomatosis is also used.

In recent years, the term multifocal papillomavirus epithelial hyperplasia has been used to define the variant that usually occurs in childhood; this variant is characterized by diffuse confluent papillomatous lesions in the oral mucosa.[3]

See also Verrucous Carcinoma, Proliferative Verrucous Leukoplakia, Cancers of the Oral Mucosa and Smokeless Tobacco Lesions.

Pathophysiology

In 1934, Kren et al[4] observed condylomatous neoplasms of the tongue, the palate, and the uvula. In 1941, Friedell and Rosenthal[5] described verrucous tumors of the buccal mucosa and the lower gingivae in 8 patients who chewed tobacco; these lesions developed in the area in which the quid of tobacco was held. Verrucous carcinoma can affect

various oroaerodigestive sites, including the esophagus,[6] the middle ear,[7] the maxillary antrum,[8,9] the nasal fossa,[10] the lacrimal duct,[11] and the bronchus.[12]

Verrucous carcinoma of both the skin and the mucosa is an uncommon low-grade squamous cell carcinoma that is clinically evident as a slowly but relentlessly enlarging warty tumor, histologically characterized by local invasion with minimal dysplasia, if any, and biologically characterized by a low incidence of metastases.[1] Even when the tumor is large, when it has been present for many years, and when it penetrates the bone, distant metastases are rare.

The typical microscopic section shows a well-differentiated typical squamous cell carcinoma with verrucous clinical morphology.[1] Ackerman initiated the clinicopathologic concept of verrucous carcinoma and described similar neoplasms of the oral cavity in 31 patients; Ackerman used the term verrucous carcinoma to denote the concept of a locally aggressive exophytic low-grade squamous cell carcinoma with little metastatic potential.[13] This tumor has also been known as florid papillomatosis, a term Rock and Fisher[14] coined in 1960. They observed multiple confluent nodules of the oral cavity and the larynx in 3 patients. In 1962, Wechsler and Fisher[15] emphasized the locally aggressive but clinically benign nature of the disease by using the term oral florid papillomatosis.

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Verrucous carcinoma of both the skin and the mucosa is an uncommon low-grade squamous cell carcinoma that is clinically evident as a slowly but relentlessly enlarging warty tumor, histologically characterized by local invasion with minimal dysplasia, if any, and biologically characterized by a low incidence of metastases.[1] Even when the tumor is large, when it has been present for many years, and when it penetrates the bone, distant metastases are rare.

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The 4 clinicopathologic types of verrucous carcinoma are as follows: (1) the anourogenital type, which includes giant condyloma acuminatum, Buschke-Löwenstein tumor, giant malignant condyloma, verrucous carcinoma of the anogenital mucosa, carcinomalike condyloma, and condylomatoid precarcinosis; (2) the oroaerodigestive type, which includes the Ackerman tumor, verrucous carcinoma of Ackerman, and oral florid papillomatosis; (3) the foot type, epithelioma cuniculatum; and (4) other cutaneous types, which include cutaneous verrucous carcinoma, papillomatosis cutis carcinoides, and papillomatosis cutis.

Oral verrucous carcinoma should be recognized as an important clinicopathologic variant of squamous cell carcinoma. Its apparent clinical benignity may result in lengthy periods of misdiagnosis, during which it is not likely to spread to distant lymph nodes. Instead, oral verrucous carcinoma is more likely to destroy the nose or the mandible as it slowly but relentlessly extends into the underlying tissue, following what appears to be the path of least resistance that often causes it to develop around regional lymph nodes and not directly involve them. To those unfamiliar with oral verrucous carcinoma, its morphologic warty or verrucous appearance and its relatively bland histologic features often suggest verruca vulgaris or pseudoepitheliomatous hyperplasia rather than squamous cell carcinoma. When the lesion extends into underlying tissues, it may occasionally be mistaken for a benign adnexal tumor or rarely an epidermoid cyst at histologic examination.

Therapy for oral verrucous carcinoma is challenging because recurrences are common, and potential anaplastic transformation after radiation therapy may be a concern.

Cyclin D1 expression in oral squamous cell carcinoma and verrucous carcinoma was found to correlate with lack of histological differentiation.[16]

Frequency

United States

Oral verrucous carcinoma is a rare neoplasm that occurs in older people. It is diagnosed in only 1-3 of every 1 million persons each year.[17] The age-adjusted average annual incidence for oral verrucous carcinoma among residents of Rochester, Minnesota, was 0.1 case per 100,000 person-years (0.2 for males, 0.0 for females), whereas the incidence for all intraoral carcinomas was 3.6 cases per 100,000 person-years (5.4 for males, 2.1 for females).

The Ackerman tumor represents 2-12% of all oral carcinomas.[18,19,20,21] In men older than 64 years, the incidence increases to 3.2 cases per 100,000 person-years; the lesion represented only 3% of the oral cancers.[17]

Verrucous carcinoma of the larynx accounts for about 1-3.8% of all primary laryngeal squamous cell carcinomas.[22,23]

International

Oral verrucous carcinoma is a rare neoplasm (see Frequency, United States, above). Verrucous carcinoma represents about 400 (5%) of 7988 primary malignancies of the oral cavity in India,[18] with most occurring in persons aged 40-50 years or older.[21]

Mortality/Morbidity

These tumors often cause considerably more morbidity than mortality.

The National Cancer Data Base includes 2350 cases of verrucous carcinoma of the head and the neck.[24]

- Most verrucous carcinomas originate in the oral cavity (55.9%) and the larynx (35.2%), and the 5-year relative survival rate is 77.9%.
- For localized verrucous carcinoma, the survival rate after surgery is 88.9% compared with 57.6% after irradiation.
- Patients receiving initial surgical treatment have a better survival rate than those treated with irradiation, especially if their lesions originated in the oral cavity.

Sex

A male predisposition is usually observed, although in one study, almost 60% of cases occurred in women.[25]

- In his original series, Ackerman documented 31 cases, 26 of which involved men.
- Although most patients (60.0%) are men, tumors of the oral cavity are more common among older females, according to the National Cancer Data Base, which includes data on 2350 cases of verrucous carcinoma of the head and the neck.[24]
- Verrucous carcinoma of the larynx is more common in men than in women.[22,23]

Age

- In Ackerman's original series, the average patient age was 67 years.
- In another survey, most patients were aged 40-50 years or older.[21]
- Most patients with verrucous carcinoma of the larynx are older than 60 years.[22,23]

Clinical

History

- The patient may note a bulky tumor.
- Some patients experience localized pain and difficulty in mastication.
- Malignant conversion of florid oral and labial papillomatosis during topical immunotherapy with imiquimod was described in one patient.[26]

Physical

The Ackerman tumor is evident as a confluence of whitish nonulcerated papillomas on the oral mucosa, often on a background of chronic irritation or leukoplakia.

- The surface may be pebbly or mamillated.[2]
- Leukoplakia may be the earliest sign.[21]
- The tumor may begin on the vermillion border of the lip or extend onto it.
- Of the 31 patients that Ackerman described, 18 had verrucous carcinoma on the buccal mucosa; 8, on the lower gingiva; 2, on the hard palate; and 1 each, on the upper gingiva, the tongue, and the tonsil.
- The most common sites are the inner aspects of the cheek along the bite line and the gingiva.
- Verrucous carcinoma slowly extends into locally contiguous sites. It may expand into the mandible or to the cheek from the inner buccal surface.
- Concurrent infection is common, and the resultant enlarged and tender lymph nodes may be mistaken for malignant involvement of the regional lymph nodes.
    - Concurrent infection can create the impression that the tumor is indurated rather than soft.
    - Despite advancement near the lymph nodes, verrucous carcinoma invariably grows around them rather than metastasizing to them.

Causes

The leading possible causes are infection with human papillomavirus (HPV) and tobacco use, especially for the Ackerman tumor. Perhaps, chemical and HPV viral co-carcinogens work together. Other factors may be important as well.

- In 1967, Barnett and Hyman[27] first linked oral florid papillomatosis to HPV on the basis of ultrastructural findings.
    - A number of HPV types are associated with squamous cell carcinoma, including HPV types 6 and 11.
    - Oral verrucous carcinomas may be associated with or caused by HPVs, particularly in individuals who are predisposed. In one study, HPV types 6 and 11 were detected in 7 of 17 cases of oral verrucous carcinoma.[28]
    - In an analysis of laryngeal verrucous carcinoma, HPV-16 DNA, HPV-18 DNA, or both were present in 13 of 29 cases.[20]
    - HPV may facilitate the development of verrucous carcinoma because of oncogenic expression.[29] The E6 oncoprotein encoded by HPV types 16 and 18 promotes the degradation of p53.[30] In addition, alterations of the amino acids in the HPV-6 E7 protein may result in HPV-16 oncoproteinlike transforming activity.[31]
- Tobacco chewing may be an etiologic factor. The possibility of chemical carcinogenesis of verrucous carcinoma of the oral cavity from tobacco has long been suggested.
    - Research has indicated that the use of chewing tobacco and snuff is strongly correlated with oral florid papillomatosis in many, but not all, patients. Why verrucous carcinomas develop in some patients and ordinary squamous cell carcinomas develop in other patients is unclear. Perhaps, some patients with oral verrucous carcinoma die from a highly aggressive second primary oral cancer due to the same carcinogenic stimuli rather than a transformation of the verrucous carcinoma.
    - In a study of 37 patients, 11 chewed tobacco and another 11 smoked tobacco.[21]
    - Among Swedish men who had oral cancer and who used snuff, almost one half had verrucous carcinoma.[32]

- Betel nuts may be linked to verrucous carcinoma,[33] although the association may be due to the tobacco added to betel chew.

- Other factors may contribute to the development of verrucous carcinoma.
  - Chronic inflammatory processes may be involved, possibly by lowering the body's mutagenic resistance.[1]
  - An important issue is whether the development of oral verrucous carcinomas is related to the patient's immune status.
  - Another risk factor is chronic inflammation or irritation such as that caused by poorly fitted dentures.

Differential Diagnoses

Acanthosis Nigricans
Oral Fibromas and Fibromatoses
Oral Granular Cell Tumors
Oral Hemangiomas
Squamous Cell Carcinoma
Viral Infections of the Mouth
Warts, Nongenital

Other Problems to Be Considered

Verrucous hyperplasia of the oral mucosa

Verruca vulgaris

Proliferative verrucous leukoplakia - A rare oral mucosa disorder that may progress to oral squamous cell carcinoma[34]

Workup

Laboratory Studies

- Ultrastructural studies may be considered.
  - Findings suggest a well-differentiated squamous cell carcinoma[35] and are similar to those of conventional squamous cell carcinomas.
  - The findings include prominent microvilli, decreased tonofilaments, and underdeveloped desmosomes.
- With oral verrucous carcinoma (VC), tissue typing for HPV may be beneficial, assuming it proves clinically useful to divide verrucous carcinomas on the basis of HPV infection.[36] In one series, HPV was identified with the polymerase chain reaction in 13 of 29 cases of laryngeal verrucous carcinoma.[20]

Imaging Studies

- The latest radiographic techniques, such as magnetic resonance imaging, should be used to define the extent of the tumor and to determine whether underlying bone or other structures are involved.
- Computed tomography can be used to demonstrate the exact location and the extent of the tumor for preoperative staging and surgical planning.

Histologic Findings

The typical microscopic section shows a well-differentiated typical squamous cell carcinoma with verrucous clinical morphology.[1]

Histologically, oral verrucous carcinoma shows exophytic and endophytic growth patterns.[1] Its massively hyperplastic and exophytic epidermis has marked hyperkeratosis, sometimes with parakeratosis. Its prominent granular layer has tumor cells that may be vacuolated, resembling and indistinguishable from the koilocytes of condylomata acuminata.

Verrucous carcinoma is characterized by blunt projections of well-differentiated epithelium supported by an edematous stroma, with chronic inflammatory cells of lymphohistiocytic origin at its infiltrating margins. These blunt tumor masses extend into the dermis and deeper structures, forming sinuses and keratin-filled cysts. Bulbous islands of benign-appearing epithelium may infiltrate the subcutaneous tissue. This deceptively

benign quality is associated with a basement membrane adjacent to its basal epithelial layer despite the composition of infiltrating tumor islands.[21]

Rare areas of focal disruption of the basement membrane are noted in oral verrucous carcinomas. Thus, neither the presence nor the absence of a basement membrane is a reliable indicator of tumor behavior. Atypical mitotic figures, individual cell necrosis, dyskeratosis, and multinucleated keratinocytes are rarely, if ever, evident. Centripetal keratinization of individual keratinocyte islands may be seen, but horn pearls are not. Individual cell cytologic features are relatively benign, with minimal dysplasia. Individual cells may be large and have big nuclei and prominent nucleoli. Occasionally, giant nuclei and enlarged malpighian keratinocytes may be evident. Intracytoplasmic glycogen is scant in verrucous carcinoma, as compared with keratoacanthoma and pseudoepitheliomatous hyperplasia.

Some oral mucosal verrucous carcinomas may be associated with small foci of floridly malignant squamous cell carcinomas,[37,38,28] adjacent ordinary squamous cell carcinomas,[39] or regional node metastases.[39,40] In one study,[37] 21 (20%) of 104 oral verrucous carcinomas had similar foci with less differentiation than that of the verrucous carcinoma. Such foci of dysplasia are associated with a doubled recurrence rate and a 10% incidence of lymph node metastases.[38] Therefore, careful sectioning to remove as much tumor as possible is indicated.

Radiation therapy has been implicated in the anaplastic transformation of some verrucous carcinomas,[40] although anaplastic transformation may represent a possible terminal event in the natural progression of verrucous carcinoma.[41] This phenomenon may be an example of a verrucous carcinoma undergoing programmed dedifferentiation to become a classic squamous cell carcinoma. The hybrid verrucous carcinoma–squamous cell carcinoma deserves careful scrutiny.

The extraoral expansion of a local tumor into the underlying cartilage and bone results in moderate dyskeratosis and numerous mitotic features as the bone is replaced by tumor. Acute and chronic inflammation and a granulation tissue reaction are also present. Tumor cells are usually not found in the blood vessels or the lymphatics; this finding is presumably correlated with the general absence of metastases in patients with mucosal verrucous carcinoma.

An ordinary squamous cell carcinoma may be a clinically silent verrucous carcinoma with histologic patterns reflecting its warty and exophytic surface. If clusters of poorly differentiated cells are present, the tumor is a conventional squamous cell carcinoma with a high malignant potential and a tendency to metastasize. However, typical verrucous carcinomas with foci of conventional squamous cell carcinoma, that is, the hybrid verrucous carcinoma–squamous cell carcinoma, may be troubling.

The distinction between verrucous carcinoma and a large and persistent verruca vulgaris may be difficult at both clinical examination and histologic examination. Verrucous carcinoma and verruca vulgaris both have the keratinocytic vacuolization that is said to be characteristic of viral warts.[42] Avoid obtaining only a small superficial skin biopsy specimen; larger specimens facilitate the correct diagnosis. Verrucous hyperplasia of the oral mucosa must also be considered; it is best evaluated in biopsy specimens obtained from the lesional margins.[43]

Treatment

Medical Care

The most prevalent treatment in the United States for verrucous carcinoma (VC) is surgery alone (69.7%), followed by surgery combined with irradiation (11.0%) and irradiation alone (10.3%).[24] Irradiation may be more common in advanced cases than in early cases (see Surgical Care).

- Surgical treatments are probably best (see Surgical Care below), and radiation therapy is generally considered a last resort.
    - In oral verrucous carcinomas, irradiation is reported to produce highly malignant behavior with metastases, but some still use this treatment with confidence.[19,41,44,45]
    - In one study, none of the 16 patients with verrucous carcinomas had features of anaplastic transformation after radiation.[45]
    - Many believe that radiation is an excellent choice for small and large oral and other types of verrucous carcinomas, with results comparable to surgery.[2,11,19,41,44]

- Combined radiochemotherapy with vinblastine, methotrexate, and bleomycin is effective in the treatment of verrucous carcinoma of the head and neck.[46] It could be successfully used with inoperable verrucous carcinoma or as an alternative to surgery.
- The possibility of anaplastic transformation due to radiation must be considered,[39] although this complication is rare. A risk factor of 10.7% is reported for anaplastic transformation of verrucous carcinoma after radiation therapy.[11] Caution is advised in the irradiation of an Ackerman tumor, except in advanced tumors for which surgical resection and other modalities are not feasible.
    - In one study, 17 cases were described. In 7 cases with oral verrucous carcinoma and 1 case with verrucous carcinoma of the nasal cavity, one of several modalities of radiation therapy was the initial treatment. Despite regression of the verrucous carcinoma with irradiation, a rapid anaplastic transformation (as seen at histologic examination) with a corresponding aggressive clinical tumor behavior developed in 3 patients, with an onset at 2, 5, and 8 months after therapy. The ionizing radiation may have produced this lethal clinical outcome.
    - Among 4 patients who underwent irradiation for oral verrucous carcinoma, anaplastic transformation developed in 1 patient, with onset at 3.5 months after treatment.[47]
    - In the studies by Perez et al[39] and Fonts et al,[47] an excellent immediate response to irradiation was followed by transformation, which was usually heralded by rapid tumor growth. Patients with similar results were described later.[48,49,50,51,52] These patients included a man with oral verrucous carcinoma who was treated with a 6-MeV linear accelerator and who developed an undifferentiated squamous cell carcinoma in the cells of the verrucous carcinoma.[48]
    - In another series of 10 patients with laryngeal verrucous carcinoma, 3 were treated with radiation. Anaplastic transformation occurred in 1 patient, who died from dissemination 10 months later.[49]
    - Patients in some of these studies had large or extensive verrucous carcinomas and seem reminiscent of those Goethals et al[53] examined in a series of 55 cases of verrucous carcinomas of the oral cavity. Three of these patients apparently died from distinct more-undifferentiated lesions that metastasized.
    - Other cases of malignant transformation have been noted.[39,41,44]
- Proton radiation therapy may induce complete regression in oral verrucous carcinoma.[50]
- Photodynamic therapy using a topical application of 20% 5-aminolevulinic acid followed by multiple 3-min fractionated irradiations with a light-emitting diode (LED) red light may be an effective and successful treatment modality for oral verrucous carcinoma.[54]
- Bleomycin iontophoretic therapy may be beneficial for lip verrucous carcinoma.[55] Intra-arterial bleomycin[56] and oral methotrexate[57] may be used to treat oral verrucous carcinoma. Intra-arterial methotrexate infusion may be effective as a primary therapy for oral verrucous carcinoma.[58]
- If HPV is determined to be an etiologic agent, the development of a subunit vaccine directed against viral oncoproteins may be a further long-term goal.[59]

Surgical Care

The most prevalent treatment in the United States is surgery alone (69.7%), followed by surgery combined with irradiation (11.0%) and irradiation alone (10.3%).[24] For oral cavity verrucous carcinomas, surgery alone is more common among early cases (85.8%) than among advanced cases (56.9%), and a larger proportion of patients with advanced disease receive irradiation alone or surgery and irradiation combined. Most laryngeal verrucous carcinomas are treated with surgery (60.3% for early disease, 55.6% for advanced disease). Compared with verrucous carcinomas in the oral cavity, laryngeal verrucous carcinomas are more often treated with radiation alone or surgery combined with radiation.

The best approach to oroaerodigestive verrucous carcinomas is probably tumor destruction combined with careful and frequent follow-up evaluations to assess for recurrence as well as separate new (and higher-grade) squamous cell carcinomas of the aerodigestive tract.

- Surgery either by means of traditional excision or a Mohs micrographically controlled excision is a popular option. The latter is a good approach in select patients.[60,61]
- Surgical diathermy, or electrocautery with thorough electrocoagulation of the tumor bed and the surrounding regions of leukoplakia or other abnormalities, is another surgical modality.[53]
- Radiation therapy has been used with surgery.[47]
- A combination of surgical excision and chemotherapy has certain advantages in oral verrucous carcinoma.[62]

Follow-up

Further Outpatient Care

- Patients with verrucous carcinoma (VC) should be carefully monitored because the following might develop:
    - Second cancer
    - Aggressive squamous cell carcinoma
    - Anaplastic transformation of a preexistent verrucous carcinoma

Complications

- Verrucous carcinoma is a locally aggressive and destructive tumor that advances into adjacent bone and other structures.
- Regional lymph node metastases occasionally occur, but distant metastases are rare.
- Rapid anaplastic transformation with widespread metastases has been described in a few patients with oral verrucous carcinoma. This complication mainly occurs after radiation therapy.

Prognosis

- See Mortality/Morbidity.
- Three hundred and two patients with oral verrucous carcinoma in India were evaluated retrospectively.[63] Early-stage tumors accounted for 39.7%; 60.4% were late-stage tumors. Sixty-eight percent (19 of 28) recurred locally; the salvage rate for recurrent tumors was 66.7% (16 of 28), with a median postrecurrence survival of 16 months (range, 10-83 mo). The 5-year disease-free survival rate after surgical therapy was 77.6%.

Patient Education

- For excellent patient education resources, visit eMedicine's Cancer and Tumors Center. Also, see eMedicine's patient education article Cancer of the Mouth and Throat.

Miscellaneous

Medicolegal Pitfalls

- A persistent wart or wartlike tumor should be evaluated to rule out verrucous carcinoma.

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