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ORIGINAL ARTICLE

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Oral verrucous carcinoma: a retrospective study in São Paulo Region, Brazil

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Abstract Oral verrucous carcinoma (OVC) is a rare variant of squamous cell carcinoma with a characteristic morphology and specific behavior. To date, few studies are available focusing the prevalence and clinicopathologic features of the oral verrucous carcinoma in Brazilian population. A total of 3,500 primary oral well-differentiated squamous cell carcinoma surgically excised in the A. C. Camargo Cancer Hospital and Amaral Carvalho Cancer Hospital, Brazil, from 1980 to 2000 were retrospectively reviewed. Twenty cases of verrucous carcinomas were identified, most of them occurring in older male with age above the sixth decade, the sites frequently affected being the lower lip and the hard palate. Microscopically, the tumor showed a heavily keratinized lesion with compressive invasion pattern, little atypia, and free surgical margins. The local recurrence was verified in 38.5% of the patients with oral verrucous carcinoma; however, regional recurrence and distant metastasis were not verified. The results suggest that, although it is less frequent and with excellent prognosis, the verrucous carcinoma presents a potential for local recurrence that should be considered during the surgical planning of this neoplasm in the oral cavity.

Keywords Verrucous carcinoma · Oral squamous cell carcinoma · Oral cancer · Verrucous lesion · Prognosis

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Introduction

Oral verrucous carcinoma (OVC) is a rare variant of squamous cell carcinoma with a characteristic morphology and specific behavior. The tumor occurs frequently in the oral cavity and larynx [4, 13, 17] but its etiopathogenesis remains unclear [2, 12, 15, 17]. Clinically, one of the intriguing aspects of this malignant tumor is its slow growth and aspect vegetant in cauliflower that can become locally aggressive if not treated [1, 5, 13, 17, 20], without any regional or distant metastasis [10, 12, 14, 17, 20].

Microscopically, this tumor first described by Ackerman [1] in 1948 is characterized by a predominant exophytic overgrowth of well-differentiated keratinizing epithelium having minimal atypia associated with intense chronic inflammatory infiltrate. In addition, locally destructive pushing margins at interface with underlying connective tissue can be found [7, 10, 12, 13, 17, 21].

The establishment of clinical or histopathological diagnosis of verrucous carcinoma in the oral cavity may be difficult to interpret. The correct diagnosis is heavily dependent on close collaboration between clinician and pathologist, and the provision to the latter of a sufficiently large biopsy specimen [2, 7, 23].

To date, few studies are available focusing the prevalence and clinicopathologic features of the OVC in Brazilian population and the samples are generally small and not representative [3, 9, 22]. The aim of this study was to evaluate, retrospectively in the period from 1980 to 2000, the clinicopathological features, outcome, and treatment of the OVCs in two centers for diagnosis and treatment of oral cancer in Brazil.

Materials and methods

A total of 7,500 squamous cell carcinomas diagnosed at the Head and Neck Surgery and Otorhinolaryngology Department of the Cancer Hospital A. C. Camargo, São Paulo, Brazil and Amaral Carvalho Cancer Hospital, Jaú, Brazil from 1980 to 2000 were retrospectively reviewed. We found 3,500 primary oral well-differentiated squamous cell carcinomas and 20 of them fulfilled the histological criteria proposed by Ackerman [1] for verrucous carcinoma.

All the patients included in this retrospective study were submitted to surgical treatment of the primary oral squamous cell carcinoma located in the tongue, floor of the mouth, retromolar area, gingiva, soft or hard palate, buccal mucosa, and lip, confirmed by biopsy. None of these patients received radiotherapy, chemotherapy, or other treatment before surgery. In addition, patients with other simultaneous primary tumors, unresectable tumors, and distant metastasis at the time of admission were excluded from the sample.

Clinical data of the patients with OVC were obtained from the medical records and included age, gender, ethnic group, tobacco and alcohol consumption, tumor location, T and N stages, treatment, and clinical follow-up (recurrence, second primary tumor, and death).

Microscopic features of the OVC were evaluated using a 5-μm-section routinely stained by hematoxylin and eosin. The tumor characteristics such as hyperchromatism, nuclear pleomorphism, keratinization, atypical mitoses, and inflammatory infiltrate were classified as absent, weak, moderate, or intense. The integrity of the basal membrane, the vascular embolization, and tumor infiltrations (muscular, bone, perineural, and glandular) was reported as absent or present.

Results

The evaluation of the 3,500 conventional well-differentiated squamous cell carcinomas located in the tongue, floor of the mouth, gingiva, retromolar area, soft and hard

Table 1 Clinical findings in 20 patients with OVC

Clinical features		Number of cases	Percentage (%)
Age	≤67 years	10	50
	>67 years	10	50
Gender	Male	11	55
	Female	9	45
Ethnic group	Caucasian	19	95
	Non-Caucasian	1	5
Tumor site	Lower lip	9	45
	Hard palate	4	20
	Soft palate	1	5
	Gingiva	3	15
	Buccal mucosa	2	10
	Tongue	1	5
Tobacco	Yes	7	35
	No	4	20
	Unknown	9	45
Alcohol	Yes	9	45
	No	–	–
	Unknown	11	55
T clinical	T1–2	13	65
	T3–4	1	5
	Unknown	6	30
N clinical	N0	20	100
	N^+	0	0
Postoperative	Yes	0	0
Radiotherapy	No	20	100
Recurrence[a]	Yes	5	38.5
	No	8	61.5
Clinical outcome	Alive, NED	9	45
	Alive, RD	0	0
	Dead due to disease	0	0
	Dead, NRD	4	20
	Lost follow-up	7	35
TOTAL		20	100

NED No evidence of disease, *RD* recurrent disease, and *NRD* not related to disease

[a]Excluding patients with lost follow-up

palate, buccal mucosa, and lips revealed that 20 were OVCs (0.57%) and 3,480 were well-differentiated squamous cell carcinomas.

Most of the patients with OVC were men (55%) and Caucasians (95%) (Table 1). The minimum age obtained on the onset of diagnosis of OVC was of 34 years and the maxim 83 years; the major occurrence of the neoplasm is observed above the sixth decade. Age varied from 54 to 83 years (mean 69 years) for female with OVC and from 34 to 83 years (mean 63.8 years) for male with OVC.

Regarding the tumor location, the OVC involved mainly the keratinized oral mucosa including the lower lip (45%), the hard palate (20%), and the gingiva (15%). Regions such as soft palate, buccal mucosa, and tongue were also affected (Table 1). In 90% of the specimens, the tumor was restricted to its original location, while in two patients the adjacent anatomical areas revealed extensive involvement.

The tabagism and etilism were found in 35 and 45% of the patients with OVCs, respectively (Table 1). Among the patients with positive history of tobacco consumption, most of them smoked paper cigarettes and a patient used pipe.

The clinical history of the OVCs with a minimum of 1 month and a maximum of 120 months was registered in 11 of the 20 patients analyzed.

Most of the tumors were classified as initial clinical stage (I–II). According to the International Union Against Cancer, 45% of the patients presented tumors T1, 20% T2, and 5% T4; it was not possible to obtain the clinical stage information of 30% of the patients. None of these patients showed regional lymph nodes involvement (Table 1).

All the patients with OVC were submitted to surgical treatment without cervical dissection, radiotherapy, and/or chemotherapy postoperative adjuvant. The local recurrence was observed in 38.5% of the patients (excluding the patients with lost follow-up) and no patient in our series developed regional or distant metastases (Table 1). A second primary tumor (OVC) in the retromolar area or buccal mucosa was detected in two patients (10%). Details regarding the clinical outcome of the patients with OVC can be visualized in Table 1.

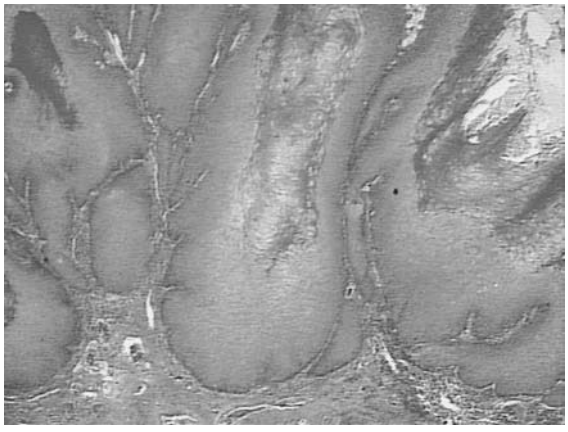

Fig. 1 The epithelium showing discrete pleomorphism and wide and long rete ridges, which seemed to push the adjacent connective tissue reflecting the little atypia of the tumor

Microscopically, 70% of the OVCs showed thickened epithelium with mild hyperchromatism, little atypia, and few figures of mitoses. The keratin-filled crypts surrounded by well-differentiated squamous epithelium with long epithelial rete ridges that seemed to "push" the adjacent connective tissue were commonly found (Fig. 1). A discrete nuclear pleomorphism was observed in 60% of the OVCs.

In the great majority of tumors (85% of OVC), basement membrane appeared to be intact. The most relevant aspect observed in the connective tissue was the presence of marked mononuclear inflammatory infiltrate in 45% of the OVCs, closely associated to neoplasm. In 50% of the tumors, the mild polymorphonuclear inflammatory infiltrate was also observed.

Vascular and/or lymphatic embolization, perineural and bone infiltrations were not observed in the OVCs, but muscular and salivary glands infiltrations were frequently detected. The surgical margins were free in all OVC analyzed in the present sample.

Discussion

In Brazil, there are few studies regarding the verrucous carcinoma in oral cavity [3, 9, 22] and most of them are related to case reports. In our retrospective study of 3,500 oral well-differentiated squamous cell carcinomas, diagnosed at the A. C. Camargo Cancer Hospital and Amaral Carvalho Cancer Hospital, São Paulo region, from 1980 to 2000, a frequency of 0.6 and 0.53% for OVC were found, respectively. This frequency is lower than those described by others, which vary from 1 to 10%, with the latter being the largest occurrence of OVC described in studies from India [2, 4, 6, 11, 17, 18, 20]. However, our results were broadly similar to a previous report of Koch et al. [13] who obtained, from 411,534 head and neck squamous cell carcinomas diagnosed in National Cancer Dates Base in the United States of America from 1985 to 1996, a total of 2,350 (0.6%) verrucous carcinomas where 1,314 (0.3%) occurred within the oral cavity.

In the present study, most OVC occurred in Caucasian men with age above the sixth decade. The anatomic areas frequently affected were the lower lip (45%) followed by the hard palate (20%), inferior gingiva (10%), and buccal mucosa (10%), as summarized in Table 1. All these demographic and clinical data are similar to the literature concerning verrucous carcinoma from multiple sites of the head and neck area, including the mouth [1, 2, 4–6, 11, 13, 14, 17, 20].

The etiology of OVCs is not completely established but it was suggested that risk factors such as tobacco use, including both inhaled and smokeless tobacco and opportunist viral activity associated with human papillomavirus, may play important roles in its pathogenesis [1, 15, 16, 18–20]. Corroborating with several other studies [2, 12, 15, 17, 20], the positive history of tobacco and alcohol in our sample were present in 35

and 45% of the patients with OVC, respectively. All the tabagists were also alcoholic and the great majority reported that they use paper cigarette and one patient uses a pipe. Moreover, the association with smokeless tobacco was not verified in patients with OVC in our sample.

Of the 20 patients with OVC, 13 of them (65%) presented lesions in the initial clinical stage (I and II) (Table 1), confirming previous findings of Jyothirmayi et al. [11] and Koch et al. [13] who showed a high frequency of verrucous carcinoma in initial clinical stage.

None of the 20 patients with OVC in the present study developed regional or distant metastasis, which confirmed the lower invasive potential of this neoplasm. According to Ferlito et al. [7, 8] and Koch et al. [13], the distant metastasis associated with verrucous carcinomas can be a consequence of an incorrect diagnosis or of the presence of foci of squamous cell carcinoma in lesions with warty features. In our sample, all the specimens with typical microscopic aspects of the VC but with focal areas of well-differentiated squamous cell carcinoma were excluded. It reinforces the idea that the appropriate biopsy is imperative to confirm the safe and reliable diagnosis of verrucous carcinoma in the oral cavity by the pathologist.

Microscopically, all OVCs presented typical features in agreement with the previously established criteria by Ackerman [1] and confirmed by others [13, 17, 21]. The tumors were exophytic, verrucoid, and with intense keratinization verified in 65% of the samples (Fig. 1).

The epithelium presented discrete pleomorphism and wide, long rete ridges, which seemed to push the adjacent connective tissue reflecting the little atypia of the tumor (Fig. 1). A histopathological feature described by McCoy and Waldron [17], Rajendran et al. [21], and those demonstrated in our sample are among the few typical mitoses figures detected in the OVC.

The integrity of basal membrane consists of an outstanding characteristic of VCs. In the present study, it was observed in 85% of oral tumors, corroborating with others findings [1, 17, 21].

An intense mononuclear inflammatory infiltrate closely associated with epithelium was frequently observed in our sample (45% of OVC). Santana Filho and Rovani [22] suggested that the presence of this mononuclear inflammatory infiltrate could constitute one of the limitation mechanisms of the invasion of this neoplasm. On the other hand, the presence of polymorphonuclear inflammatory cells in 80% of our sample can be reflecting the presence of secondary infection put upon to the neoplasm, as the candidosis as previously reported [10, 24]. For Jacobson and Shear [10], the stagnation areas in the nonkeratinized surface crevices may induce a polymorphonuclear leukocyte infiltration into the epithelium itself and this in turn may produce an atypical epithelial appearance.

Although the VC is frequently curable in the precocious stage, this neoplasm can become locally aggressive if not treated, and may invade the muscle, bone, salivary gland, and cartilage. In the present study, muscular and salivary gland infiltrations were frequently found in OVCs. Rajendran et al. [21] reported 53% of invasion of bone, muscular, and glandular tissues.

All the patients with OVC were submitted to surgical treatment and none of them received radiotherapy or/and chemotherapy postoperative adjuvant. The presence of a second primary tumor was verified in 10% of the patients with OVC; this is similar with the frequency observed by Kraus and Perez-Mesa [14] who verified a second primary tumor in 8 (10.4%) out of 77 OVCs analyzed.

Regarding the clinical outcome of the patients, we verified that 38.5% of the patients with OVC presented local recurrence of the tumor; this recurrence rate is close to the one reported by Jacobson and Shear (40%) but it was larger than those described by Ackerman (29%), Jyothirmayi et al. (30.1%), Kraus and Perez-Mesa (6.93%), and Rajendran et al. (6.12%).

Some authors [11, 13] found high rates of local recurrence and worse survival rates for patients with OVC who received radiotherapy as initial treatment and they suggested that these recurrences probably represent peripheral extensions of the tumors incompletely eradicated. According to Jacobson and Shear [10] and McCoy and Waldron [17], the slow growth and lower invasive potential of the OVC could induce inadequate surgical treatment, making the surgical margins compromised. However, this hypothesis was not reinforced in our sample because all verrucous carcinomas presented free surgical margins confirmed by histopathological analyses. These results suggest that OVC seems to have an intrinsic potential for local recurrence and prolonged follow-up may be necessary after surgical excision.

In conclusion, the analysis of the OVCs in Brazilian patients showed that although it is not frequent and has excellent prognosis, this neoplasm presents a potential for local recurrence that should be considered during surgical planning in the oral cavity. Finally, it is important to reinforce that appropriate diagnosis of the OVC can prevent the most extensive involvement of adjacent areas and/or wide surgical resection of the tumor.

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