Oral verrucous lesions: Controversies in diagnosis and management

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ABSTRACT

Aims: Oral verrucous lesions, typically presenting as slowly enlarging, grey or white, warty, exophytic overgrowths on the buccal mucosa or gingiva may be verrucous carcinoma (VC), verrucous hyperplasia (VH), proliferative verrucous leukoplakia (PVL), or may show the conventional invasive pattern of squamous cell carcinoma (SCC). This study was undertaken with the aim to report the demography of different types of oral verrucous lesions and evaluate their long-term outcome.

Material & methods: This clinical study comprised 15 patients with verrucous lesions of the oral cavity who underwent biopsy for confirmation of diagnosis.

Results: Among these, 12 (80%) were male and only three (20%) were female. The age distribution ranged from 32 to 74 years with a median age of 45 years at the time of diagnosis. The most common site of VC within the oral cavity was the buccal mucosa (46.7%). 5 were proven cases of VC, 3 PVL and 7 VH. All cases of VH, PVL were managed by surgical excision, while VC was managed by surgical excision with superficial ostectomy followed by two cycles of chemotherapy additionally, if micro-invasion was observed on histopathological examination. The 2-year overall survival and tumour control rate was 93.4%. Recurrence was not seen in any patient till the time of analysis at a follow up of 3–5 years.

Conclusion: Accurate diagnosis of the verrucous lesions is important and should be differentiated from grade I squamous cell carcinoma. Management should be based upon the nature, behaviour and malignant potential of the lesion.

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Keywords: Verrucous carcinoma, Verrucous hyperplasia, Proliferative verrucous leukoplakia, Squamous cell carcinoma

INTRODUCTION

Oral verrucous lesions, typically presenting as slowly enlarging, grey or white, warty, exophytic overgrowths on the buccal mucosa or gingiva of older men, fall into different categories. Lesions with a verrucous surface may be verrucous carcinoma (VC), verrucous hyperplasia (VH), proliferative verrucous leukoplakia (PVL), or may show the conventional invasive pattern of squamous cell

carcinoma (SCC) with an exo-endophytic growth pattern or be the hybrids. It is a frequent problem for clinicians to differentiate among them because of their extensive nature mimicking an invasive cancer.¹ Often the invasion can be lacking in incisional biopsies, hence an underlying conventional carcinoma cannot be excluded. An important help could be offered by molecular approaches.

VC shows the characteristic cell kinetics of normal epithelium and not of conventional squamous carcinoma.

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Received: 13.9.2012; Accepted: 15.10.2012

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<http://dx.doi.org/10.1016/j.jobcr.2012.10.006>

S-phase is confined to basal layer, unlike the invasive cancer. By flow cytometry, VC is a diploid lesion; on the contrary, the conventional squamous cancer often shows aneuploidy and genomic instability.²

This study aims to discuss the controversy surrounding diagnosis of various oral verrucous lesions and their treatment outcomes.

MATERIALS & METHODS

This clinical study comprised 15 cases who visited our outpatient department between 2007 and 2009 with verrucous lesions of the oral cavity. Written informed consent was obtained from patients prior to inclusion. The study was approved by the Institutional Ethical Committee. After recording medical and dental history, dietary habits, socio-economic status, thorough clinical examination and routine investigations were carried out for biopsy of the lesions. Further management was provided and outcome was assessed at regular 6 monthly period (ranging 2–4 years). VH and PVL were treated by surgical excision, whereas VC was managed by surgical excision followed by 2 cycles of chemotherapy, if needed (Table 1).

RESULTS

Of the 15 patients identified with oral verrucous lesions, 12 (80%) were male and only three (20%) were female. The age distribution ranged from 32 to 74 years with a median age of 45 years at the time of diagnosis. The most common

site of VC within the oral cavity was the buccal mucosa, 46.7% (Figs. 1 and 2).

All patients underwent biopsy, of which 5 were proven cases of VC, 3 of PVL and 7 were cases of VH. All cases of PVL (Figs. 3 and 4) and VH (Figs. 5 and 6) were managed by surgical excision, while VC was managed by surgical excision with superficial ostectomy followed by two cycles of chemotherapy additionally, if micro-invasion was observed on histopathological examination. The 2-year overall survival and tumour control rate was 93.4%. Recurrence was not seen in any of our case in the primary site or neck area till the time of analysis.

DISCUSSION

The term “verrucous” has been applied for lesions showing a keratotic exophytic surface composed of sharp or blunt epithelial projections with keratin-filled invaginations (plugging), but without obvious fibrovascular cores. VC, a warty variant of squamous cell carcinoma is characterized by a predominantly exophytic overgrowth of well-differentiated keratinizing epithelium. 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.^{1,3} The associated basement membrane appears intact³ (Table 2). 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 “verrucoid” features, (b) proliferative verrucous leukoplakia (PVL), (c) reactive keratosis and epithelial

Table 1 Oral verrucous lesions and their outcome.

S N	Age/sex	Site	Diagnosis	Treatment	Outcome
1	65/M	Buccal mucosa	VH	Surgical excision	Surviving, healthy
2	40/M	Buccal mucosa	VC	Surgical excision, chemotherapy	Surviving, healthy
3	36/F	Palate	VC	Surgical excision, chemotherapy	Surviving, healthy
4	32/M	Buccal mucosa	PVL	Surgical excision	Surviving, healthy
5	44/F	Buccal mucosa	VC	Surgical excision, chemotherapy	Surviving, healthy
6	60/M	Buccal mucosa	VH	Surgical excision	Surviving, healthy
7	55/M	Buccal mucosa	VH	Surgical excision	Surviving, healthy
8	74/M	Alveolus	VH	Surgical excision	Surviving, healthy
9	42/M	Alveolus	VC	Surgical excision with superficial ostectomy	Surviving, healthy
10	45/M	Buccal mucosa	VH	Surgical excision	Surviving, healthy
11	48/M	Alveolus, labial vestibule	VC	Surgical excision, chemotherapy	Expired after 1st cycle of chemotherapy
12	42/M	Commissure	PVL	Surgical excision	Surviving, healthy
13	52/M	Commissure	VH	Surgical excision	Surviving, healthy
14	43/F	Palate	VH	Surgical excision	Surviving, healthy
15	47/M	Labial mucosa	PVL	Surgical excision	Surviving, healthy

Fig. 1 Clinical photograph of a conformed case of verrucous carcinoma (VC).

hyperplasia, (d) pseudoepitheliomatous hyperplasia, (e) verruca vulgaris, and (f) keratoacanthoma when verrucous carcinoma affects cutaneous sites and their hybrids. Hybrid carcinomas should be staged and managed as conventional

SCC because of their metastatic potential, contrary to classical VC which shows excellent prognosis following complete surgical removal in the early stages.⁴

Hansen et al⁵ classified the pathological process of PVL into 10 grades, i.e., normal oral mucosa (0), homogeneous leukoplakia (2), verrucous hyperplasia (4), verrucous carcinoma (6), papillary squamous cell carcinoma (8), and poorly differentiated carcinoma (10), in which the odd scores refer to a status intermediate between those referred to by the adjacent even scores.

Proliferative verrucous leukoplakia (PVL) has been described, as a distinct and aggressive type of oral leukoplakia with unknown aetiology.⁵ It affects women more commonly in the sixth decade (female to male ratio = 4:1), occurring predominantly on the buccal mucosa, palate, gingiva, and tongue. Its rate of malignant transformation is extremely high.⁵ PVL shows slow and persistent growth but can become malignant, on average within 4.7 years,⁶ 6.1 years⁵ or take up to 11.6 years⁷ to become cancerous. The process is irreversible and usually progresses to cancer. Batsakis et al⁸ found SCC occurrence in almost 100% of proliferative verrucous leukoplakia, an observation also corroborated by Silverman⁷ and Bagan,⁶

Fig. 2 a: Histopathological section from verrucous carcinoma lesion (2×) showing epithelium in verrucous pattern with parakeratin plugging. b: (4×) showing elongation and thickening of rete pegs with parakeratin crypts descending into the rete ridges appearing as elephant feet. c: (10×) showing individual cells which do not display any atypia, although mild basilar hyperplasia and mild parabasal hyperchromatism are evident.

Fig. 3 Clinical photograph of a conformed case of proliferative verrucous leukoplakia (PVL).

who found malignant transformation in 87% and 63.3% PVL. Also, PVL has a high tendency to recur after treatment. Once PVL is confirmed, active therapy should be undertaken, such as surgery, laser management, photodynamic therapy, combined treatments, etc. However, PVL responds poorly to various therapeutic measures, and its recurrence rate is relatively high, even after its surgical removal.⁹

Verrucous hyperplasia (VH) may be associated with papillomas or be a *de novo* lesion. VH and PVL are irreversible clinicopathologic lesions with considerable

Fig. 4 Histopathological section from proliferative verrucous leukoplakia lesion (10×) showing thickened parakeratinized epithelium with acanthotic spinous layer and focal rete peg showing dysplastic changes including basilar hyperplasia, altered nuclear–cytoplasmic ratio and parabasal cell hyperchromatism.

Fig. 5 Clinical photograph of a conformed case of verrucous hyperplasia (VH).

potential for evolving into verrucous or squamous cell carcinoma. PVL is a disease of the oral cavity in which VH is a part of its developmental spectrum. Human papillomavirus, as a cofactor, may play an important role in some of the lesions. Verrucous hyperplasia is considered to be an early form of verrucous carcinoma and recommended to be treated accordingly.¹⁰

In a study by Keszler,¹¹ histologic data showed orthokeratinization more frequently in PVL and VH, while parakeratinization in VC. Although, sharp epithelial projections predominated in all three lesion types, lympho-plasmatic infiltration and Russell bodies were more frequent in VH. Histometrically, connective tissue–epithelial interface, epithelial height and connective tissue–epithelial interface plus verrucous epithelial surface, showed statistical differences between PVL or VH versus VC. Keszler concluded that histometric analysis was able to detect epithelial differences between both premalignant lesions and VC.¹¹

Verrucous carcinoma (VC) was defined as a diagnostically problematic squamous cell neoplasia involving lip, oropharyngeal, and laryngeal mucosa and named as “Ackerman’s tumour” by Ackerman, 1948 who reported 31 patients with ‘VC’ of the oral cavity.¹² VC is a rare, slow-growing tumour that enlarges with direct extension rather than frank invasion. They are chiefly exophytic, do not metastasize, but can invade and destroy deeper tissues.¹³ The lesser aggressive nature of VC establishes it as a low grade, well-differentiated variant of oral SCC with an excellent prognosis and indolent clinical behaviour. Having said that, the clinical behaviour of VC can be, at times, destructive despite its deceptively benign microscopic appearance: papillomatosis, acanthosis, dysplasia in variable degrees.^{8,13} Although it is rare and associated

Fig. 6 a: Histopathological section from verrucous hyperplasia lesion (4×) showing hyperplastic epithelium lying above the adjacent normal epithelium. b: (10×) showing hyperkeratinized epithelium with parakeratin plugging. c: (20×) showing individual cells which do not display any atypia or any dysplastic features.

with an excellent prognosis, VC has an intrinsic potential for local recurrence that should be considered when planning surgery.¹⁴ Observations show their tendency to recur in the form of less-differentiated carcinomas.¹⁵ Metastatic spread occurs late, if at all.^{3,14} Contradictory observations have been published concerning the metastatic potential of oral VC. Some authors describe an invasive growth with disconnected islands and groups of invading tumour cells and therefore a capacity to demonstrate metastasis¹⁶ and described sporadic cases of metastatic VC, while others insist that VC is locally invasive and cannot metastasize.² Regional lymph node involvement is uncommon in VC, while adjacent structures are often involved as it often acquires large dimensions during tumour progression.¹⁷

The reported rate of VC among all types of squamous cell carcinoma is 2–9%,¹⁸ while it comprises approximately 3% of all primary invasive carcinomas of the oral mucosa.¹⁹ In

the oral cavity, the most common sites for VC are vestibule, buccal mucosa, hard palate.¹⁴ It represents 1–4% of laryngeal malignancies, in the vocal cords. Other sites reported in head and neck region include paranasal sinus, scalp, nasopharynx, oesophagus and temporal bone.^{20,21} It is so uncommon that verrucous carcinoma composes only 5% of tumours at these sites.²¹ In Greece, the reported incidence for VC among other intraoral malignancies is 5.8%.²² Although the mucous membranes of the head and neck are the most common sites of VC development, this tumour may also be found on other cutaneous surfaces including the anorectal region, external genitals and skin of the extremities, particularly the sole of the foot.¹⁴ This uncommon lesion, in its pure form, can be considered a disease of later life, typically occurring in the seventh–eighth decades, with a strong male predominance. VC is strongly associated with the chronic use of tobacco, chewing betel nuts, alcohol and poor oral hygiene.²¹

Table 2 Comparison of clinicopathologic features and prognosis of squamous cell carcinoma (SCC), verrucous hyperplasia (VH), proliferative verrucous leukoplakia (PVL) and verrucous carcinoma (VC).

<i>Histologic types of cancer</i>	SCC	VH	PVL	VC
Clinical features	Ulcerated	Exophytic, cauliflower like	Cauliflower like	Cauliflower like
Preferred site	Tongue, floor of mouth		Buccal mucosa, palate, gingiva, tongue	Buccal mucosa, hard palate
Histologic features	Variable degree of keratinization	Orthokeratinization Lympho-plasmatic infiltration and Russell bodies. Atypia or dysplastic changes absent	OrthoKeratinization. Atypia or dysplastic changes present	Intense parakeratinization “elephant feet” like downgrowth compressing underlying connective tissue Minimal or absent cytological atypia Basement membrane appears intact ³
Malignant transformation	—	Low	High	Moderate
Metastatic potential	High	None	None	Absent/late
Prognosis	Poor	Excellent	Excellent	Excellent

According to recent studies, human papillomavirus could have a potential role in the tumoural development and progression, although this topic is still under discussion.⁴ A more acceptable hypothesis is that opportunist viral activity associated with chronic tobacco and alcohol consumption may be involved in the pathogenesis of this neoplasm.¹⁴

Some investigators have described “hybrid” lesions, when they present the dominant microscopic features of VC, but also contain small areas of tumour invasion typical of conventional SCCs.^{23,24} However, others consider the presence of tumour invasion towards the histopathologic diagnosis of SCC, to dictate clinical treatment. Although adequate surgical excision remains the treatment of choice for the oral VC, chemotherapy, alone or in combination with radiotherapy, has also been employed as initial treatment. Radiation therapy alone has been contraindicated due to the possibility of anaplastic transformation from oral VC to more aggressive SCC.¹⁴

CONCLUSION

Accurate diagnosis of VC still remains an important problem. It should be differentiated from other benign lesions such as verrucous leukoplakia, papilloma, pseudoeitheliomatous hyperplasia, verrucous hyperplasia, as well as from grade I squamous carcinoma. It is important to exclude the latter possibility, hence deeply infiltrating portions of the lesion should be excised during biopsy.

VC of the oral cavity is a different clinicopathologic tumour distinguished from the usual squamous cell carcinoma because of its local invasiveness, non-metastasizing behaviour, and special clinical appearance.

CONFLICTS OF INTEREST

All authors have none to declare.

ACKNOWLEDGEMENT

We would like to thank Dr. S. Gupta for providing legend for histopathological sections.

REFERENCES

1. Woolgar JA, Triantafyllou A. Pitfalls and procedures in the histopathological diagnosis of oral and oropharyngeal squamous cell carcinoma and a review of the role of pathology in prognosis. *Oral Oncol.* 2009;45(4–5):361–385.
2. Ferlito A, Antonutto G, Silvestri F. Histological appearances and nuclear DNA content of verrucous squamous cell carcinoma of the larynx. *ORL J Otorhinolaryngol Relat Spec.* 1976;38(2):65–85.
3. Pindborg JJ, Reichart PA, Smith CJ, van der Wall IWHO. *Histological Typing of Cancer and Precancer of the Oral Mucosa.* 2nd ed. Berlin: Springer-Verlag; 1997:10–16.
4. Santoro A, Pannone G, Contaldo M, et al. A troubling diagnosis of verrucous squamous cell carcinoma (“the bad kind” of keratosis) and the need of clinical and pathological correlations: a review of the literature with a case report. *J Skin Cancer.* 2011;2011. <http://dx.doi.org/10.1155/2011/370605>. Article ID 370605.
5. Hansen LS, Olson JA, Silverman S. Proliferative verrucous leukoplakia: a long-term study of thirty patients. *Oral Surg Oral Med Oral Pathol.* 1985;60:285–298.

6. Bagan JV, Jimenez Y, Sanchis JM, et al. Proliferative verrucous leukoplakia: high incidence of gingival squamous cell carcinoma. *J Oral Pathol Med*. 2003;32(7):379–382.
7. Silverman S, Gorsky M. Proliferative verrucous leukoplakia: a follow-up study of 54 cases. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod*. 1997;84:154–157.
8. Batsakis JG, Suarez P, el-Naggar AK. Proliferative verrucous leukoplakia and its related lesions. *Oral Oncol*. 1999;35(4):354–359. Review.
9. Ge L, Wu Y, Wu L, et al. Case report of rapidly progressive proliferative verrucous leukoplakia and a proposal for aetiology in mainland China. *World J Surg Oncol*. 2011;9:26.
10. Murrah VA, Batsakis JG. Proliferative verrucous leukoplakia and verrucous hyperplasia. *Ann Otol Rhinol Laryngol*. 1994 Aug;103(8 Pt 1):660–663.
11. Keszler A, Gutierrez R, Dominguez FV. Verrucous carcinoma, hyperplasia and leukoplakia of the oral mucosa: a clinico-histopathological and histometric study. *Acta Odontol Latinoam*. 1985;2(2):43–51.
12. Rajendran R, Varghese I, Sugathan CK, Vijayakumar T. Ackerman's tumour (verrucous carcinoma) of the oral cavity: a clinico-epidemiologic study of 426 cases. *Aust Dent J*. 1988;33:295–298.
13. Tomb R, El-Hajj H, Nehme E, Haddad A. Verrucous carcinoma of the tongue occurring on lesions of lichen planus. *Ann Dermatol Venereol*. 2003;130(1 Pt 1):55–57.
14. Pereira MC, Oliveira DT, Landman G, Kowalski LP. Histologic subtypes of oral squamous cell carcinoma: prognostic relevance. *J Can Dent Assoc*. 2007;73(4):339–345.
15. Medina JE, Dichtel W, Luna MA. Verrucous-squamous carcinomas of the oral cavity. A clinicopathologic study of 104 cases. *Arch Otolaryngol*. 1984;110:437–440.
16. Schrader M, Laberke HG. Differential diagnosis of verrucous carcinoma in the oral cavity and larynx. *J Laryngol Otol*. 1988;102:700–703.
17. Asproudis I, Gorezis S, Aspiotis M, et al. Orbital metastasis from verrucous carcinoma of the oral cavity: case report and review of the literature. *In Vivo*. 2007;21:909–912.
18. Ogawa A, Fukuta Y, Nakajima T, et al. Treatment results of oral verrucous carcinoma and its biological behaviour. *Oral Oncol*. 2004;40:793–797.
19. Bouquot JE. Oral verrucous carcinoma. Incidence in two US populations. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod*. 1998;86:318–324.
20. McCoy JM, Waldron CA. Verrucous carcinoma of the oral cavity. A review of forty-nine cases. *Oral Surg Oral Med Oral Pathol*. 1981;52:623–629.
21. Miller ME, Martin N, Juillard GF, Bhuta S, Ishiyama A. Temporal bone verrucous carcinoma: outcomes and treatment controversy. *Eur Arch Otorhinolaryngol*. 2010;267:1927–1931.
22. Zavras AI, Laskaris C, Kittas C, Laskaris G. Leukoplakia and intraoral malignancies: female cases increase in Greece. *J Eur Acad Dermatol Venereol*. 2003;17:25–27.
23. Barnes L, Eveson JW, Reichart P, Sidransky D. Oral cavity and oropharynx. In: Barnes L, Everson JW, Reichart P, Sidransky D, eds. *World Health Organization Classification of Tumours. Pathology and Genetics of Head and Neck Tumours*. Lyon: International Agency for Research on Cancer Press; 2005:164–208.
24. Niparko JK, Rubinstein MI, McClatchey KD. Invasive squamous cell carcinoma within verrucous carcinoma. *J Otolaryngol*. 1988;17(1):38–40.