

Verrucous carcinoma of the oral cavity: a clinico-pathologic appraisal of 133 cases in Indians

K. P. Rekha · Punnya V. Angadi

Published online: 16 April 2010
© Springer-Verlag 2010

Abstract

Introduction Verrucous carcinoma (VC), a rare variant of squamous cell carcinoma is an established entity with distinctive morphology and specific clinical behavior. To date, only a small series of head and neck verrucous carcinomas have been reported in the literature.

Materials and methods The present study evaluated 133 cases of verrucous carcinoma for the age, sex, site of involvement, duration of disease at the time of diagnosis, associated habits and common presenting symptoms, presence of other mucosal lesions, recurrence, and the histopathology.

Results and discussion Verrucous carcinoma accounted for 16.08% among oral squamous cell carcinoma compared to 2–12% reported in the literature. VC was more common in males with greater predilection to buccal mucosa due to widespread use of tobacco chewing in Indian scenario. Age distribution was lower as compared to other studies with prominence in the fifth decade. Mandibular involvement was more frequent as compared to those in literature.

Conclusion Development of recurrence following radiotherapy in few cases supports anaplastic changes by radiotherapy.

Keywords Verrucous carcinoma · Clinicopathologic · Histopathologic · Management

Introduction

Verrucous carcinoma (VC), a variant of squamous cell carcinoma (SCC) is an established entity with characteristic morphology and specific clinical behavior. The lesion was first described by Ackerman in 1948 [1] as a carcinoma with very limited capacity to invade and rare metastatic potential. The preferred site for verrucous carcinoma in head and neck region include the oral cavity (75%) followed by the larynx (15%) [2]; however; similar lesions have also been described in different sites such as skin, uterine cervix, bladder, ano-rectal region, genitalia, and esophagus [3, 4].

In the oral cavity per se, verrucous carcinomas are relatively rare; representing only 2% to 12% of all oral epithelial malignancies [5–9]. The most frequently involved sites being the buccal mucosa, gingiva, and alveolus [7, 10]. These tumors show a predilection for elderly males (fifth to seventh decade) [11, 12], particularly individuals who are tobacco chewers, snuff dippers, or heavy smokers [13–15].

The tumor exhibits a distinctive slow exophytic growth producing cauliflower-like warty lesion which is locally aggressive but well circumscribed. Although the adjacent cervical lymph nodes are often enlarged, regional and distant metastases rarely occur in this tumor [2, 16].

Although VC has distinct clinical and histopathological features, the diagnosis may often be difficult, clinically, due to similar appearing lesions like verrucous hyperplasia, proliferative verrucous leukoplakia, and squamous cell carcinoma while histopathologically, due to insufficient biopsy specimen [6, 17].

K. P. Rekha
Department of Oral and Maxillofacial Pathology
and Microbiology, SDM College of Dental Sciences,
Dharwad 580009 Karnataka, India

P. V. Angadi
Department of Oral and Maxillofacial Pathology
and Microbiology, KLE VK Institute of Dental sciences,
Nehru Nagar, Belgaum 590010, India

P. V. Angadi (✉)
Department of Oral Pathology,
KLE VK Institute of Dental sciences, Nehru Nagar,
Belgaum 590010 Karnataka, India
e-mail: punnya_angadi@rediffmail.com

Histologically, the lesion is a highly differentiated one with little or no cytologic atypia/mild dysplasia. They demonstrate extreme thickening of epithelium with clefts lined by parakeratotic plugging, bulbous rete ridges pushing rather than invading into with an intact basement membrane and chronic inflammatory changes in the underlying connective tissue [17].

Surgical excision is considered as the treatment of choice for the oral VC [3, 18]. However, chemotherapy alone [19, 20] or in combination with radiotherapy [21, 22] has also been employed as initial treatment.

To date, only a small series of head and neck verrucous carcinomas have been reported in the literature. The largest reported experience comes from India, where oral cancer forms the most common malignancy (27% of all cancers) [18]. However, there are only few studies on the frequency and clinico-pathological feature of verrucous carcinoma in the Indian population in recent years. Hence, this study was carried out to establish the relative incidence and clinico-pathologic data on verrucous carcinoma over a period of 18 years from a region of Southern India.

Materials and methods

All cases of verrucous carcinoma diagnosed since 1989 were retrieved from the files of Department of Oral Pathology, SDM College of Dental Sciences, Dharwad. The clinical information relevant to the tumors were documented including age, sex, site of involvement, duration of disease at the time of diagnosis, associated habits, common presenting symptoms, presence of other mucosal lesions, and recurrence. Two experienced oral

pathologists (R and P) reviewed all the cases histopathologically and transformation of previously diagnosed verrucous carcinomas to squamous cell carcinoma was also evaluated.

Results

A total of 827 cases of oral squamous cell carcinoma were diagnosed and treated in S.D.M. College of Dental Sciences, Dharwad, between 1989 and 2007 out of which 133 (16.08%) patients were diagnosed as verrucous carcinoma and included in this study.

Of the 133 patients, 103(77.44%) were males and rest were females 30 (22.55%) giving a male to female ratio of 3.4:1. Verrucous carcinoma occurred in patients of wide age range of 30–85 years (Fig. 1) with peak incidence in fifth and sixth decades (27.06%). The mean age of occurrence was around 53 years with no significant difference observed between males (52.74) and females (53.86).

The site distribution of verrucous carcinoma is shown in Table 1. Extension of lesion to adjacent site was noted in most cases. The buccal mucosal lesions were seen extending into the sulcus and eventually destroying the bone (11.42%, 8/70). Likewise, the lesions arising in lower alveolus were extending into floor of the mouth and buccal mucosa (27.77%, 5/18). In retrospect, the most widely involved area is identified as the site for documentation. The correlation of site with sex predilection revealed that in almost all sites, there was a male predominance and lesions on tongue and maxillary sinus were seen exclusively in males (Table 1).

Fig. 1 Graph demonstrating the sex distribution for incidence of verrucous carcinoma

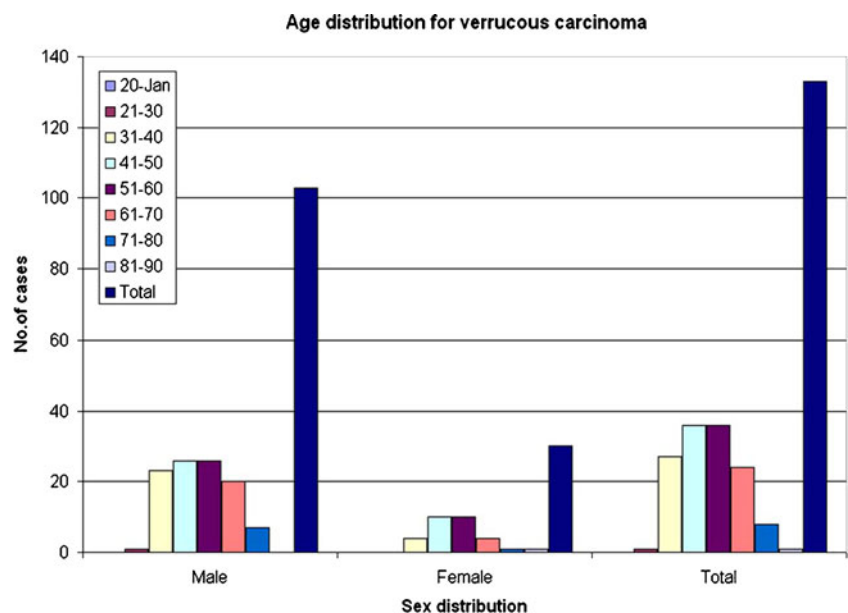


Table 1 Anatomical distribution of oral verrucous carcinoma

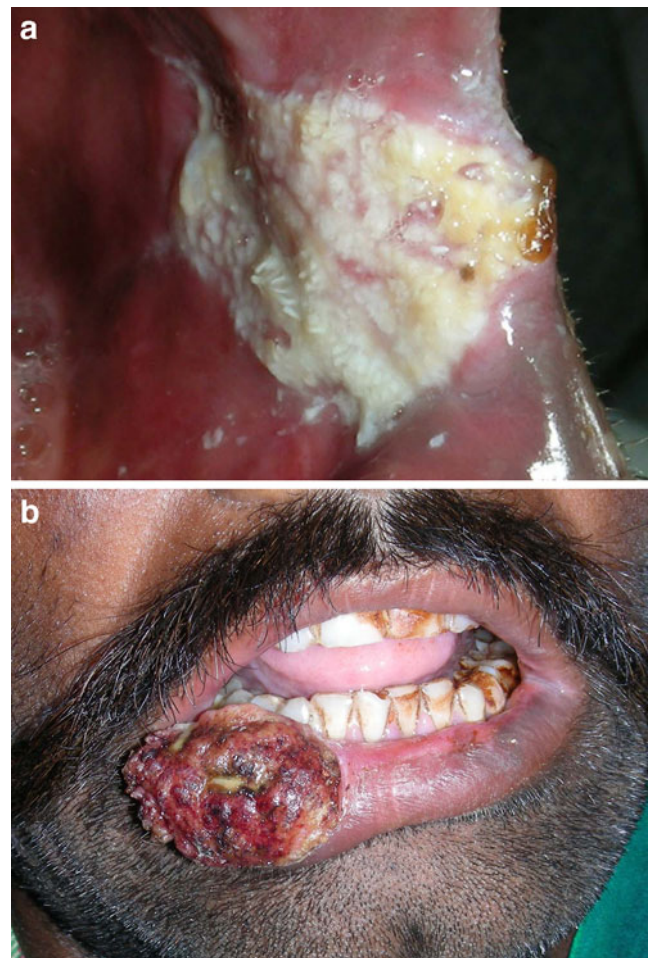
Site	M	F	Total
Buccal mucosa	54	16	70
Lower alveolus	13	5	18
Retromolar region	10	2	12
Palate	4	2	6
Lip	4	3	7
Tongue	6	0	6
Gingiva	3	1	4
Upper alveolus	7	1	8
Maxillary sinus	2	0	2
Total	103	30	133

Majority of the lesions were asymptomatic and clinically presented as an ulcero-proliferative (78), nonulcerated exophytic lesion [13], patch [7], and nodules [14]. Details on clinical presentation were not available for 21 cases (Fig. 2). Only few patients had symptoms like pain and inability to open mouth. Most VCs were nonmetastatic and were staged based on size. Available data showed 41.35% had T2 lesions and 12 (9.02%) patients each had T1 and T4 lesions. Only eight (6.01%) patients were in T3 stage. Clinically palpable lymph nodes were evident in few cases (15.03%) with bilateral involvement noted in a single case.

The duration of the tumor at the time of diagnosis was provided only in 94 cases and average time at presentation was 3 years with one case having duration of 20 years.

Most verrucous carcinomas occurred in soft tissue; however, it can involve the bone resulting in superficial erosion and destruction. The present series showed superficial erosion [5], bone loss [10], extensive destruction [5], and extension of lesion to coronoid process [2]. Mandibular involvement (5.26%) was also evident radiographically in lesions of buccal mucosa [6] and lower lip [1].

Figure 3 gives the distribution and risk of various habits in verrucous carcinoma cases. Use of smokeless tobacco in the form of Pan/Betel quid chewing (51.13%) was the most frequent habit in the study group followed by habits in combination (18.79%) which included chewing and smoking (17/25–68%), chewing and alcohol (6/25–0.24%) as well as smoking and alcohol (0.75%) Only a single case had all three habits. Other habits were smoking of either beedis/cigarettes (9.02%) or use of alcohol alone (0.75%). A surprising finding was lesions were also seen to have developed in patients without habits (20.30%). In relation to sex, chewing Pan/Betel quid was the most frequent habit in both genders. However, smoking and habits in combination was exclusively seen in males. An interesting correlation observed was that non-habit-related lesions were predominant in males (Fig. 3). Association of habits in verrucous

**Fig. 2** Clinical photograph of verrucous carcinoma of buccal mucosa (a) and lip (b)

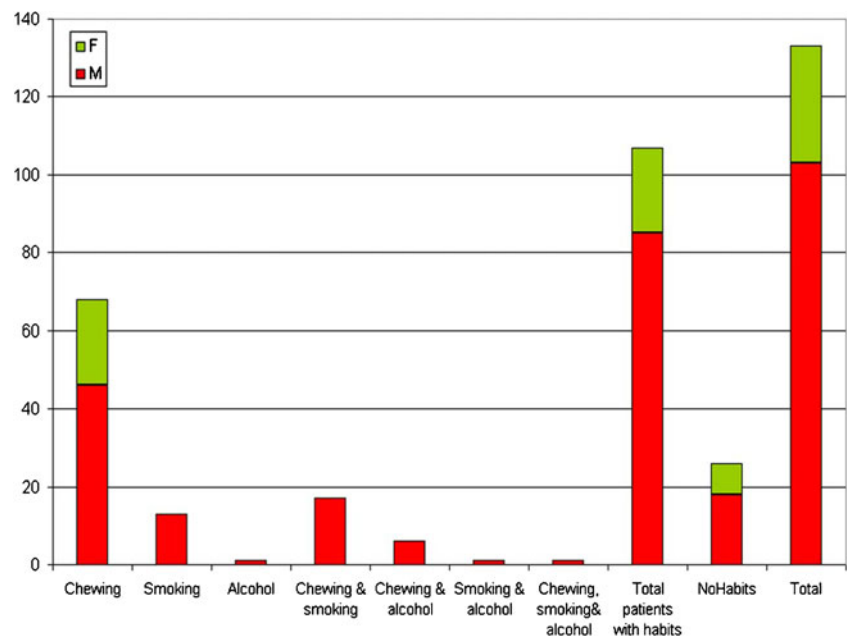
carcinoma was analyzed with regards to the site (Fig. 4). Buccal mucosa was the predominant site affected in patients who practiced both chewing (52.85%) and multiple habits (22.85%). All other sites also showed increased prevalence for chewing habit except gingival involvement (75%) seen in patients with smoking habit.

Another observation made was, few cases of verrucous carcinoma (3%, 4/133) developed between 6 months to 4 years following radiotherapy treatment rendered for squamous cell carcinoma. These patients except one had quit all habits.

An additional finding was presence of other associated lesions like squamous cell carcinoma [2], leukoplakia [6], oral submucous fibrosis [6], oral lichen planus [1], and candidiasis [1] was noticed in our study.

Majority of cases of verrucous carcinoma were treated surgically. Radical neck dissection (RND) was performed in patients with clinical lymphadenopathy. RND was also performed in few patients with clinically N₀ neck. This was based on the large size of the lesion, clinical aggressive-

Fig. 3 Graph showing the associated habits in males and females



ness, noncompliance to suggestion of cessation of smoking/chewing habits, and difficulties with regular follow-up. In few patients; surgery and radiotherapy was performed.

Histologically, most of the cases showed predominantly hyper-parakeratinized epithelium proliferating in a papillary form and extending deep into the connective tissue with broad and bulbous rete ridges showing pushing margins. Clefts lined by parakeratin, minimal dysplasia, and an intact basement membrane were also observed. Some cases showed severe degree of dysplasia and extension up to

the muscle layer. Chronic inflammatory cells predominantly lymphocytes, few multinucleated giant cells resembling Langhans, and foreign body type were seen in the underlying connective tissue (Fig. 5). Histopathological evaluation of clinically palpable lymph nodes revealed normal follicles, lymphoid hyperplasia [10], and tuberculosis [2].

Recurrence was seen in 2.25% of cases (3/133) which developed after 1–4 years of treatment; and two of which developed following radiotherapy.

Fig. 4 Shows the site distribution of oral verrucous carcinoma in relation to habits

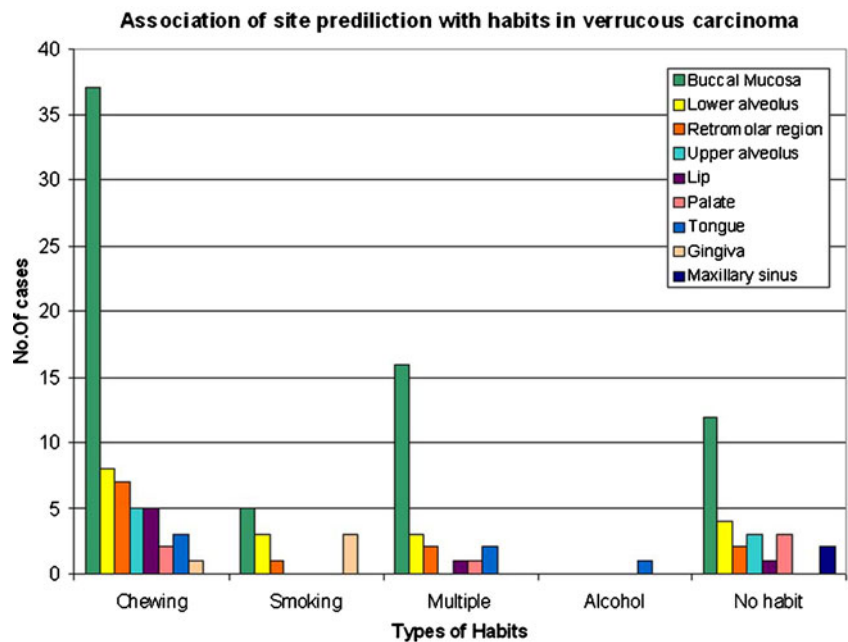
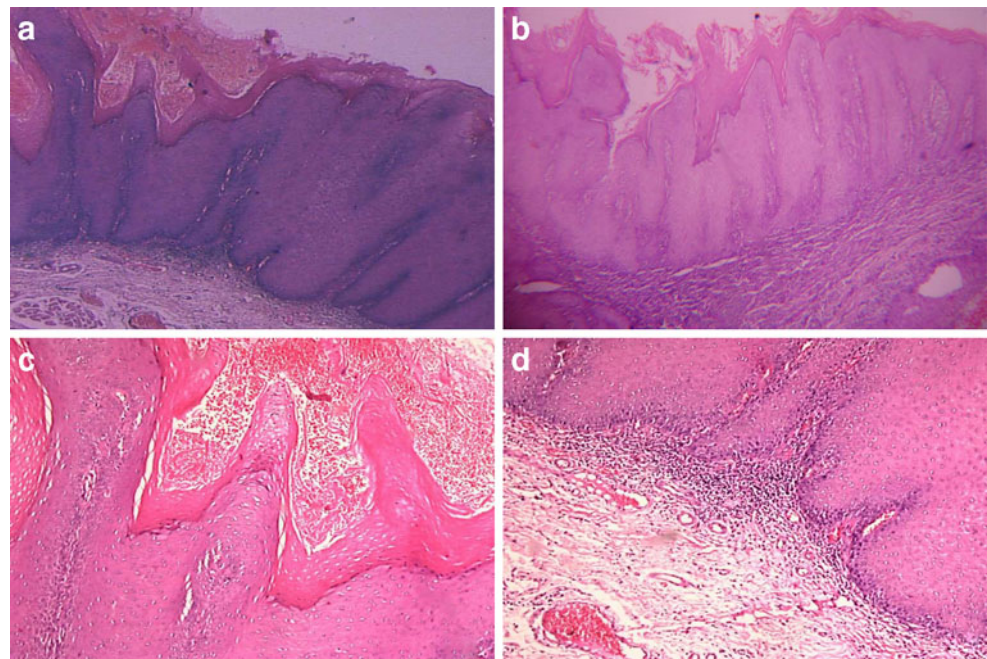


Fig. 5 Photomicrograph demonstrating hyper-parakeratinized epithelium proliferating in a papillary form and extending deep into the connective tissue with broad and bulbous rete ridges showing pushing margins (a and b). Clefts lined by parakeratin are seen (c). d Demonstrates minimal dysplasia, an intact basement membrane and chronic inflammatory cells in sub-epithelial connective tissue



Discussion

Ackerman first recognized verrucous carcinoma in 1948 [1] as a distinct clinicopathologic entity and described it as a specific type of squamous cell carcinoma with distinct histopathologic and clinical findings. Various factors have been implicated in the development of VC, including chemical carcinogens, trauma, chronic irritation, and human papilloma virus. This retrospective analysis aims to describe the incidence, demographic features, patterns of presentation, etiologic factors, the treatment modalities, and outcomes for verrucous carcinoma of the oral cavity, as experienced in a teaching institute in Southern India.

Although oral VC is considered rare worldwide, we found a frequency of 16.08% of verrucous carcinoma among oral squamous cell carcinomas, much higher than the previous reports [5, 8, 9, 23, 24].

The age distribution of verrucous carcinoma in the present study was lower (52.28 years) than the previous reports [2, 23] in previous studies, females presented with VC at a significantly older age (75 years) as compared with males (67 years) [2, 5]. However, we did not find a significant age difference between males (52.53 years) and female (53.86 years). Interestingly, in 36.8% of cases; VC occurred in patients below 50 years. The incidence of VC earlier in life as shown in the present study could be attributed to the accelerated aging process in developing countries due to poor nutrition, life style, and health care.

With regards to sex predilection, the result of the present study was consistent with overall male predominance (77.44%) as reported by various authors [12, 15, 24].

However, few studies have reported female predominance [2, 8, 25].

As reported by many authors [7, 8, 10, 26], the most common location was buccal mucosa (52.6%) followed by lower alveolus (13.5%). Retromolar region was the other common site noticed in the present study. However, several authors have shown lower lip and the hard palate also to be the frequently affected sites [11, 24]. Involvement of adjacent structures is common in long-standing verrucous carcinomas and involvement of mandible was reported in range of 1.2% to 19.6% [18, 26, 27]. Our study showed 24.8% (33/133) of VC with mandibular involvement. This suggests that the clinical behavior of VC can be destructive despite its deceiving benign microscopic appearance [2].

The common clinical presentation of the lesions as a painless ulcerative, exophytic cauliflower growth seen in this study is consistent with the general description of the lesion in various reports [1, 3, 8, 16, 20]. But few cases presented as patches in our survey signifying that these lesions may present initially as leukoplakia before progressing to a more exophytic growth as reported by Kamath et al. [11].

VC have been reported to be an indolent lesions with very limited capacity to invade at least until late in its history [17]. The duration of the tumor at the time of diagnosis was provided only in 94 cases and the average interval at presentation was 3 years with one case having 20 years duration suggesting it to be a long-standing and slow-growing lesion. The delay in detection may be attributed to the fact that these lesions do not cause any discomfort to the patient apart from their mass. Majority of

the cases in our study too were asymptomatic while few presented with pain and inability to open the mouth.

Lymphadenopathy reported in VC has usually been thought to represent reactive hyperplasia secondary to inflammatory reaction [16]. The cervical lymphadenopathy seen in our patients (15%) could be due to poor oral hygiene and coexistent infections (tuberculosis) as reported by Ackerman [1].

The pathogenesis of this neoplasm has been associated with malignant conversion from benign verrucous lesions [2] and chemical carcinogens, especially tobacco chewing [2, 3, 18]. Batsakis et al. [16] consider verrucous carcinoma to be a part of a histologic spectrum of leukoplakia with verrucous hyperplasia. Some consider verrucous hyperplasia as a morphologic variant of VC [28] or as an irreversible precursor of VC [16].

Chemical carcinogens have long been implicated in the etiology of oral verrucous carcinoma [3]; but identification of a specific etiologic factor is often difficult because of incidence of multiple habits like use of smoking and smokeless tobacco along with alcohol. The most significant role in the pathogenesis of VC has been associated with use of chewing tobacco and snuff dipping [13, 14]. The habitual chewing of “paan,” a mixture of betel leaf, lime, betel nuts, and tobacco, has been extensively implicated for the high incidence of verrucous type of oral cancers in India [29]. The present study showed that 69.9% (93/133) of the patients had the habit of chewing tobacco, with or without other aetiological risk factors such as smoking and consumption of alcohol. The lesions often occurred in the buccal mucosa which was the regular site of placement of the quid. Smoking alone was associated with VC in 9% while multiple habits were seen in 18.8% of the cases. Alcohol, another carcinogen in VC was hardly observed in the present study. These findings supports the role of chemical carcinogens especially tobacco in the development of verrucous carcinoma in this part of country.

An interesting and notable finding was occurrence of VC in patients without any habits (20.30%) consistent with previous reports [30]. This implies that other factors may be responsible for the development of these carcinomas which include poor oral hygiene, local irritation, and low socioeconomic status [24, 31]. A probable relation between oral VC and human papilloma virus has also been suggested. According to Eisenberg [32], the opportunistic viral activity associated with chronic tobacco and alcohol consumption may be involved in the pathogenesis of this neoplasm. Molecular genetic alterations may also play a role in the pathogenesis of VC [33]. We were unable to establish a precise causative factor in non-habit-associated lesions. However, radiotherapy can be considered as one of the contributory factors in few of the verrucous carcinoma (3.1%) in the present study.

Verrucous carcinoma is often associated with other mucosal lesions, especially squamous cell carcinoma, leukoplakia, chronic candidiasis, and lichen planus [11, 31]. VC, in our series was also seen in association with similar lesions and in addition with oral submucous fibrosis. These could be attributed to widespread migration of an altered cell throughout the mucosa or to prolonged exposure of the oral epithelium to carcinogens leading to the independent transformation of multiple epithelial cells at diverse sites demonstrating a field cancerization phenomenon [34].

Histopathological appearance of VC was similar to various reports [16, 17] and showed a well-differentiated stratified squamous epithelium exhibiting finger-like projection with minimal or no cytologic atypia, deep surface invaginations/clefts filled with parakeratin or orthokeratin, deep bulbous rete ridges with pushing margins, and intact basement membrane. Dense chronic inflammatory infiltration consisting of lymphocytes and plasma cells in the superficial lamina propria and occasional leakage of keratin eliciting a foreign body giant cell reaction was also evident.

VC should be differentiated histologically from similar appearing lesions like verrucous hyperplasia and proliferative verrucous leukoplakia. All these lesions show atypical epithelial hyperplasia with varying degrees of dysplasia. The VC lacks the well-formed, wide papillary fronds of a squamous cell papilloma. Lack of atypia and intact basement membrane helps to rule out conventional SCC and papillary SCC from VC. There have been accounts of squamous cell carcinoma occurring in VC described by several authors and as many as 20% cases show invasive/micro-invasive carcinoma in a part of the lesion [12]. This raises a question whether such lesion is a hybrid lesion or transition of VC to SCC or part of continuum of conventional SCC [16].

Additionally, other problems encountered in precise diagnosis of VC are the inadequate depth of biopsy and papillary growth that prevent the assessment of invasion in VC. In our study also, 20 cases, which were earlier diagnosed as VC with invasion, turned out to be SCC on subsequent excisional biopsy. So we are of the opinion that lesions with presence of tumor invasion in VC should definitely be given a histopathological diagnosis of squamous cell carcinoma. This emphasizes the role of clinicians in proving a proper clinical assessment and obtaining adequate depth of biopsy from a representative area. Though pathologists are justifiably uneasy in giving a diagnosis of VC, evaluation of multiple samples from the excised specimen may aid in coming to an accurate diagnosis.

Various treatment options have been attempted for oral verrucous carcinoma; principal among them being surgical excision. Considerable controversy exists regarding ana-

plastic transformation in VC following radiotherapy [35, 36]. However, others consider radiotherapy to be an effective mode of treatment in these tumors [21]. In our study, four cases of squamous cell carcinoma treated by surgery and radiotherapy presented with recurrent lesion showing features of verrucous carcinoma and three cases of recurrent verrucous carcinoma probably represented the effects of radiotherapy.

The local recurrence of oral VC has been reported frequently in the range of 30–50% [2, 22, 26, 31], although it is rare and is usually associated with an excellent prognosis following excision. In our institute, the protocol followed is that VC is managed similar to SCC with thorough excision of the lesion and radical neck dissection for lesions presenting with lymphadenopathy. This far-reaching approach could be responsible for the low rate of recurrence (three cases) seen in our series.

Conclusion

This study provides a data on verrucous carcinoma as obtained in South Indian population. Verrucous carcinoma accounted for 16.08% among oral squamous cell carcinoma compared to 2–12% reported in the literature. In agreement with other reported series, VC was more common in males with greater predilection to buccal mucosa due to widespread use of tobacco chewing in Indian scenario. Age distribution was lower as compared to other studies with prominence in the fifth decade. Mandibular involvement was more frequent as compared to those in literature. Development of verrucous carcinoma following radiotherapy in few cases supports anaplastic changes by radiotherapy. Further epidemiological research should be carried out for understanding the frequency and distribution of VC in different races and different geographic areas to further define its biologic profile.

Acknowledgments We thank the Oral and Maxillofacial Surgery team of SDM College of Dental Sciences and Hospital, Dharwad, especially Dr. Gopalkrishnan K. for the biopsy referrals to our department and Dr. C. Bhasker Rao, Principal for the guidance and support.

References

- Ackerman LV (1948) Verrucous carcinoma of the oral cavity. *Surgery* 23:670–678
- Koch BB, Trask DK, Hoffman HT, Lucy H, Karnell LH, Robinson RA, Zhen W et al (2001) National survey of head and neck verrucous carcinoma. Patterns of presentation care and outcome. *Cancer* 92:110–120
- Spiro RH (1998) Verrucous carcinoma, then and now. *Am J Surg* 176(5):393–397
- Ferlito A, Recher G (1980) Ackerman's tumor (verrucous carcinoma) of the larynx. A clinicopathologic study of 77 cases. *Cancer* 46:1617–1630
- Bouquot JE (1998) Oral verrucous carcinoma: incidence in two US populations. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 86:318–324
- Goethals PL, Harrison EG, Devine KD (1963) Verrucous squamous carcinoma of the oral cavity. *Annals Surg* 106:845–847
- Medina JE, Dichtel W, Luna MA (1984) Verrucous- squamous carcinoma of the oral cavity. *Arch Otolaryngol Head Neck Surg* 110:437–440
- McCoy JM, Waldron A (1981) Verrucous carcinoma of the oral cavity. A review of forty-nine cases. *Oral Surg, Oral Med Oral Pathol* 52:623–629
- Rajendran R, Varghese I, Sugathan CK (1988) Ackerman's tumour (verrucous carcinoma) of the oral cavity: a clinic-epidemiological study of 426 cases. *Aust Dent J* 23:295–298
- McDonald JS, Crissman JD, Gluckmen JL (1982) Verrucous carcinoma of the oral cavity. *Head Neck Surg*; 5:22–28
- Kamath VV, Varma RR, Gadewar DR, Muralidhar M (1989) Oral verrucous carcinoma. An analyses of 37 cases. *J Craniomaxillofac Surg* 17:309–314
- Sundstrom B, Mornstad H, Axell T (1982) Oral carcinomas associated with snuff dipping. Some clinical and histological characteristics of 23 tumors in Swedish males. *J Oral Pathol* 11(3):245–251
- Wray A, Mc Guirt WF (1993) Smokeless tobacco usage associated with oral carcinoma. Incidence, treatment, outcome. *Arch otolaryngol Head and Neck Surg* 119:929–933
- McGuirt WF (1983) Snuff dipper's carcinoma. *Arch Otolaryngol Head Neck Surg* 109:757–790
- Jacobson S, Shear M (1972) Verrucous carcinoma of the mouth. *J Oral Pathol* 1(2):66–75
- Batsakis JG, Hybels R, Crissman JD, Rice DH (1982) The pathology of head and neck tumors. Verrucous carcinoma. Part 15. *Head Neck Surg* 5:29–38
- Odell EW, Morgan PR (1998) Biopsy pathology of oral tissues. Champmen and Hall Medical, London, pp 229–233
- Rajendran R, Sugathan CK, Augustine J, Vasudevan DM, Vijayakumar T (1989) Ackerman's tumour (verrucous carcinoma) of the oral cavity: a histopathologic study of 426 cases. *Singapore Dent J* 14(1):48–53
- Sheen MC, Sheu HM, Lai FJ (2004) A huge verrucous carcinoma of the lower lip treated with intra-arterial infusion of methotrexate. *Br J Dermatol* 151(3):727–729
- Chen HM, Chen CT, Yang H (2005) Successful treatment of an extensive verrucous carcinoma with topical 5-aminolevulinic acid-mediated photodynamic therapy. *J Oral Pathol Med* 34(4):253–256
- Jyothirmayi R, Sankaranarayanan R, Varghese C, Jacob R, Nair MK (1997) Radiotherapy in the treatment of verrucous carcinoma of the oral cavity. *Oral Oncol* 33(2):124–128
- Yoshimura Y, Mishima K, Obara S (2001) Treatment modalities for oral verrucous carcinomas and their outcomes: contribution of radiotherapy and chemotherapy. *Int J Clin Oncol* 6(4):192–200
- Ogawaa A, Fukutaa Y, Nakajimaa T (2004) Treatment results of oral verrucous carcinoma and its biological behaviour. *Oral Oncol* 40:793–797
- Oliveira DT, Moraes RV, Fiamengui F (2006) Oral verrucous carcinoma: a retrospective study in São Paulo Region, Brazil. *Clin Oral Investig* 10(3):205–209

25. Tornes K, Bang G, Stromme Koppang H, Pedersen KN (1985) Oral verrucous carcinoma. *Int J Oral Surg* 14(6):485–492
26. Walvekar RR, Chaukar DA, Deshpande MS (2009) Verrucous carcinoma of the oral cavity: a clinical and pathological study of 101 cases. *Oral Oncol* 45:47–51
27. Vidyasagar MS, Fernandes DJ, Pai Kasturi D, Akhileshwaran R, Rao K, Rao S (1992) Radiotherapy and verrucous carcinoma of the oral cavity. A study of 107 cases. *Acta Oncol* 31(1):43–47
28. Slootweg PJ, Muller H (1983) Verrucous hyperplasia or verrucous carcinoma. An analysis of 27 patients. *J Maxillofac Surg* 11(1):13–19
29. Kolbusz RV, Goldberg LH (1994) Verrucous carcinoma of the oral cavity. *Int J Dermatol* 33:618–622
30. Neville BW, Damm DD, Allen CM (1995) Oral and maxillofacial pathology. W.B. Saunders, Philadelphia, pp 304–306
31. Kraus FT, Perezmesa C, Kraus FT, Perez-Mesa C (1966) Verrucous carcinoma: clinical and pathologic study of 105 cases involving oral cavity, larynx and genitalia. *Cancer* 19:26–38
32. Eisenberg E, Rosenberg B, Krutchkoff DJ (1985) Verrucous carcinoma: a possible viral pathogenesis. *Oral Surg Oral Med Oral Pathol* 59(1):52–57
33. Drachenberg B, Blanchaer R, Joffe OB (1997) Comparative study of invasive squamous cell carcinoma and verrucous carcinoma of the oral cavity, expression of bcl-2, p53, and Her-2/neu, and indices of cell turnover. *Cancer Detect Prev* 21:483–489
34. Bedi GC, Westra WH, Gabrielson E (1996) Multiple head and neck tumours: evidence for a common clonal origin. *Cancer Res* 56:2484–2487
35. McCaffrey TV, Witte M, Ferguson MT (1998) Verrucous carcinoma of larynx. *Ann Otol Laryngol* 107:391–395
36. Tharp ME, Shidnia H (1995) Radiotherapy in the treatment of verrucous carcinoma of head and neck. *Laryngoscopy*; 104:391–396