Multi Centricity of Oral Verrucous Carcinoma: A Case Series of 22 Cases

Sandhya Gokavarapu · Nagendra Parvataneni · C. R. Charan ·
Sreenivasa Puthamakula · Ganesh Kulkarni · B. Sridher Reddy

Received: 28 November 2014 / Accepted: 30 January 2015 / Published online: 13 February 2015
© Association of Otolaryngologists of India 2015

Abstract Verrucous carcinoma (VC) is an uncommon variant of squamous cell carcinoma characterized by proliferative outgrowing clinical appearance of the tumor. Incidence of VC is 2–12 % among oral cancers, the true incidence of VC can be accessed only from surgically treated cases since thorough processing of the entire tumor is necessary for accurate diagnosis, foci of invasive squamous cell carcinoma are found often in the substance of these tumors, thus, over reporting of this tumor is not uncommon. The retrospective data of a tertiary cancer hospital was analysed to understand the clinical challenges and outcome of patients with VC. The frequent association of VC with second primary oral cancer (22.7 %) observed in

our series highlights the multi centricity of carcinogenesis in these patients.

Keywords Verrucous carcinoma · Oral cancer

Introduction

Verrucous carcinoma (VC) is an uncommon variant of squamous cell carcinoma characterised by proliferative outgrowing clinical appearance of the tumor, it was first described by Ackermann in 1948 and hence known as Ackermann's tumour [1]. Incidence of VC is 2–12 % among oral cancers [2]. However, Medina et al. [3] has reported that 20 % of VC cases consists of invasive component co existing within them, thus, the true incidence of this tumor can be accessed only from surgically treated cases. Currently the tumours with synchronous VC and SCC within same maternal field are referred to as hybrid VC (Fig. 1).

VC is reported to occur in the oral cavity, larynx, pyriform sinus, esophagus, nasal cavity paranasal sinuses, external auditory meatus, lacrimal duct, skin, scrotum, penis, vulva, vagina, uterine cervix, perineum, and the leg, among them, oral cavity is the most frequent site of occurrence.

VC is seen more frequently in males above sixth decade of life [4].

Clinical appearance of the tumor often shows large areas of involved mucosa with regional lymphadenopathy; however, seldom these lymph nodes reveal tumor on pathological examination [5].

Classic VC microscopically consists of minimal atypia and locally destructive pushing margins at its interface with underlying connective tissue; it is often difficult to

S. Gokavarapu (✉) · N. Parvataneni · C. R. Charan ·
S. Puthamakula · G. Kulkarni · B. S. Reddy
Basavatarakam Indo American Cancer Hospital and Research
Centre, Hyderabad 500034, Andhra Pradesh, India
e-mail: sandhyagokavarapu@gmail.com

N. Parvataneni
e-mail: nparvataneni@gmail.com

C. R. Charan
e-mail: charanreddy24@yahoo.com

S. Puthamakula
e-mail: drsreenivasams@yahoo.com

G. Kulkarni
e-mail: dr.ganesh.kulkarni@gmail.com

B. S. Reddy
e-mail: drsridherb@gmail.com

C. R. Charan · G. Kulkarni
Malla Reddy College of Dental Sciences, Hyderabad, India

B. S. Reddy
Government Dental College and Hospital, Hyderabad, India

Fig. 1 Verrucous carcinoma clinical picture

differentiate VC from Verrucous hyperplasia. Verrucous hyperplasia consists of exophytic overgrowth of well differentiated keratinizing epithelium that is similar to VC but without destructive pushing border at its interface with the underlying connective tissue, differentiation of this pattern is best possible from biopsies performed at the advancing edge of the tumor where basement membrane of the adjacent normal mucosa is evident to compare [6]. However; communication between pathologist and surgeon is often necessary.

The aetiology of VC is unknown but its association with tobacco use and more recently with HPV subtypes of 6, 11, 16 and 18 describe them as a potential risk factors [7].

Current paper describes clinic-pathological features of VC along with association of premalignant changes and second primary oral cancer in 22 patients of VC.

Case Series

Historical cohort of patients treated from January 2010 to December 2012 were analysed, 892 patients were treated surgically at a Tertiary Cancer Centre for oral cancer in this period of whom 22 patients of VC were isolated for this series.

Patients with history of previous surgery for premalignant lesions were included in the series. However, patients with recurrent VC after previous surgery or radiation were not included. The median period of follow up was 37 months.

Age ranged from 21 years to 76 years; there were 10 female (45.4 %) and 12 (55.65) male patients, pathological tumor staging showed 4 (18 %) patients with T1, 13 (59 %) with T2, 3 (13.6 %) with T3 and 2 (9 %) T4 tumours.

19 (86.3 %) reported history of tobacco consumption in various forms illustrated in Table 1.

Site distribution revealed 13 (59 %) patients with tumour over buccal mucosa, five (22.7 %) patients over tongue, two lower lip, one each over upper lip and angle of the mouth. nine (total of 18 % of cases on lip subset).

Margin status of the series revealed six (27.2 %) patients with clear adequate margin status of more than 5 mm histological clearance, 15 (68.1 %) patients with close margins (1–5 mm) and one (4.5 %) patient had involved margin on initial resection which was revised under intra operative frozen section control.

Six (27.2 %) patients had association of premalignant lesion along with the primary tumour in the same maternal field (four verrucous hyperplasia and two dysplasia).

One patient presented with synchronous verrucous hyperplasia.

Total 5 (22.7 %) patients had second primary oral cancer—four (18.1 %) patients had synchronous second primary cancer along with VC (one patient had synchronous VC and three with synchronous well differentiated squamous cell carcinoma. Table 1) and one patient developed metachronous second primary cancer and is currently alive with locally advanced locoregional disease.

Seventeen patients underwent neck dissection, five patients did not undergo neck dissection, all 17 patients were N0 on histology, and among them 14 (82.3 %) patients showed reactive hyperplasia in the lymph nodes on the histology.

Total two (9 %) patients died, overall survival was 90.9 % in current series. Disease free survival was 86.3 %.

One patient had local recurrence with invasive squamous cell carcinoma and died of subsequent disease metastasis to neck and skeleton (patient no 21 in Table 1) on 18th month post surgery, another patient died on 43rd month post surgery without evidence of Locoregional recurrence (patient no 2 in Table 1).

Discussion

VC has been known to be associated with use of chewable forms of tobacco; current evidence supports its association with HPV virus, though numerous studies described different subtypes of HPV; the association of events resulting in subsequent tumor genesis is still under evaluation [7].

Most of the studies and case series describe occurrence of VC in elderly individuals with mean age of above sixth

Table 1 Demographic, clinical and pathological data of the patients with primary VC of oral cavity

S no	Age	Sex	Tobacco use	Site	Stage	Reconstructive flap	Note on neck nodes	Margin status	Premalignant lesion within tumor substance	Presence of synchronous premalignant lesions	Synchronous 2nd primary cancer	Metachronous 2nd primary cancer	Grade of 2nd primary cancer	Local recurrence	Mortality	Follow up period	Site of second lesion
1	54	M	Gutka	Buccal mucosa	T4	PMMC	Reactive hyperplasia of enlarged nodes	2 mm	No	Verrucous hyperplasia	Absent	Absent	Not applicable	Absent	Alive	46	Ipsilateral buccal mucosa
2	44	F	Jarda	Buccal mucosa	T3	PMMC	Reactive hyperplasia of enlarged nodes	1 mm	Dysplasia	No	Present	Absent	WDSCC	Absent	Dead	43	Ipsilateral buccal mucosa
3	50	F	No history	Buccal mucosa	T2	PMMC	Reactive hyperplasia of enlarged nodes	8 mm	No	No	Absent	Absent	Not applicable	Absent	Alive	42	–
4	65	F	Jarda pan	Angle Of mouth	T1	Primary closure	Neck dissection not done	5 mm	No	No	Present	Absent	Verrucous carcinoma	Absent	Alive	42	Upper lip
5	52	M	Gutka	Buccal mucosa	T2	PMMC	Reactive hyperplasia of enlarged nodes	2 mm	No	No	Absent	Present	WDSCC	Absent	Alive	41	Contralateral buccal mucosa
6	48	M	Jarda	Buccal mucosa	T2	Microvascular osseo cutaneous fibula	Reactive hyperplasia of enlarged nodes	2 mm	No	No	Absent	Absent	Not applicable	Absent	Alive	40	–
7	31	M	Jarda pan	Buccal mucosa	T2	PMMC	Reactive hyperplasia of enlarged nodes	Involved revised	Verrucous hyperplasia	No	Absent	Absent	Not applicable	Absent	Alive	38	–
8	50	F	Jarda	Buccal mucosa	T2	PMMC	No significant finding in neck nodes	2 mm	Verrucous hyperplasia	No	Absent	Absent	Not applicable	Absent	Alive	36	–
9	62	M	Cutta	Buccal mucosa	T4	PMMC	No significant finding in neck nodes	13 mm	Dysplasia	No	Absent	Absent	Not applicable	Absent	Alive	33	–
10	49	M	Gutka, Jarda pan	Buccal mucosa	T3	PMMC, Abby eslander's flap	Neck dissection not done	2 mm	No	No	Absent	Absent	Not applicable	Absent	Alive	32	–
11	68	M	No history	Lower lip	T3	Abby eslander's flap	Reactive hyperplasia of enlarged nodes	5 mm	No	No	Absent	Absent	Not applicable	Absent	Alive	31	–
12	55	F	No history	Lower lip	T2	Primary closure	Neck dissection not done	8 mm	No	No	Absent	Absent	Not applicable	Absent	Alive	30	–
13	34	M	Jarda pan	Buccal mucosa	T2	PMMC	Reactive hyperplasia of enlarged nodes	1 mm	No	No	Absent	Absent	Not applicable	Absent	Alive	29	–

Table 1 continued

S no	Age	Sex	Tobacco use	Site	Stage	Reconstructive flap	Note on neck nodes	Margin status	Premalignant lesion within tumor substance	Presence of synchronous premalignant lesions	Synchronous 2nd primary cancer	Metachronous 2nd primary cancer	Grade of 2nd primary cancer	Local recurrence	Mortality	Follow up period	Site of second lesion
14	73	F	Jarda pan	Buccal mucosa	T2	PMMC	Reactive hyperplasia of enlarged nodes	4 mm	No	No	Absent	Absent	Not applicable	Absent	Alive	20	–
15	21	M	Gutka	Buccal mucosa	T2	PMMC, Abby eslander's flap	No significant finding in neck nodes	12 mm	No	No	Absent	Absent	Not applicable	Absent	Alive	20	–
16	76	F	Jarda pan	Upper lip	T1	Primary closure	Reactive hyperplasia of enlarged nodes	7 mm	No	No	Present	Absent	WDSCC	Absent	Alive	15	Ipsilateral lower lip
17	55	F	Jarda pan	Lateral margin of the tongue	T1	Primary closure	Neck dissection not done	5 mm	Verrucous hyperplasia	No	Present	Absent	WDSCC	Absent	Alive	40	Contra lateral margin of the tongue
18	61	M	Cigarette	Lateral margin of the tongue	T2	No reconstruction	Reactive hyperplasia of enlarged nodes	8 mm	Verrucous hyperplasia	No	Absent	Absent	Not applicable	Absent	Alive	36	–
19	74	F	Jarda pan	Lateral margin of the tongue	T2	No reconstruction	Reactive hyperplasia of enlarged nodes	4 mm	No	No	Absent	Absent	Not applicable	Absent	Alive	28	–
20	40	M	Jarda pan	Buccal mucosa	T2	PMMC	Reactive hyperplasia of enlarged nodes	3 mm	No	No	Absent	Absent	Not applicable	Absent	Alive	26	–
21	45	F	Jarda pan	Lateral margin of the tongue	T2	No reconstruction	Reactive hyperplasia of enlarged nodes	3 mm	No	No	Absent	Absent	Not applicable	Recurred	Dead	18	–
22	76	M	Gutka	Lateral margin of the tongue	T1	No reconstruction	Neck dissection not done	4 mm	No	No	Absent	Absent	Not applicable	Absent	Alive	19	–

WDSCC: Well differentiated squamous cell carcinoma

PMMC: Pectoralis major myocutaneous flap

Gutka: complex mixture of betel nut, tobacco and slaked lime

Jarda: dried processed tobacco leaf

Pan: pack of fresh betel leaf, betel nut and slaked lime

Cutta: Indian cigar

decade of the life [4]. Mean age in our series was 53.7 years.

Male to female ratio in the published data varied from male predominance [4] to equal sex prediction and some studies with female predominance [8] our series shows 45 % female 55 % male cases.

Most of published reports showed buccal mucosa as predominant site of occurrence [4] followed by gingiva, buccal mucosa most frequently involved in current series, however; second most frequent site was lateral margin of oral tongue followed by lip.

Most frequent stage of presentation in our series was T2, T1 and T2 presentation was more common in study by Oliveira et al. [9]. However; some series showed advanced staged clinical presentation in more frequency [4].

82.3 % of cases showed cervical lymphadenopathy with reactive hyperplasia in current series, Tornes K et al. [5] noted that most of the clinically palpable nodes in these cases were inflammatory cervical lymphadenopathy, although neck dissection is not frequently done in cases of VC, our cases underwent neck dissection in situations where a complex reconstruction was required such as suspicious lymphadenopathy with large tumors or presence of synchronous second primary oral cancer, however; all these cases underwent elective neck dissections limited to level I to III for buccal mucosa subsets or level I to IV for oral tongue cases.

A frequent association of premalignant and malignant lesions were noted in our cases. The term synchronous is used when a second primary either existed at the time of surgery or developed within six months of initial surgery. When the second primary tumour developed after six months of the initial surgery, it was referred as metachronous.

Difficulty and ambiguity in the diagnosis resulting in repeated biopsies, association of this tumor with other premalignant and malignant related conditions and the requirement of access to neck vasculature for reconstruction were some of the factors considered for decision on performing the elective neck dissection in this series.

Association with premalignant change and second primaries were observed; history of tobacco use and wide spread field changes have some influence in this regard, Slaughter's description of field cancerization where in, multiple foci of cancer arise from condemned mucosa was inferred by Akkerman et al. [1]. Akkerman et al. [1] reasoned recurrence of this tumor to the existing predisposition of the epithelium towards malignancy. Overall 5 (22.7 %) patients in our series had synchronous or metachronous second primary oral cancer, these numbers are greater to Walvekar R et al. [4], who reported 6.9 % of incidence of second primary among oral VC patients.

15 (68.1 %) of our cases had close margins and one patient had involved margin on initial resection (revised under intra operative frozen control), however; only one patient died of locoregional recurrence.

Historically; Monoclonal origin of second primary tumor was proved in certain cases of Bedi, Gauri C., et al. [9] this strengthened the hypothesis by Worsham et al. [10] who described lateral arborisation of cancer from single focus, suggesting second cancer in patients with premalignant change indeed is recurrence, it appears, as though, VC needs attention in this regard. Further research is necessary to understand this rare tumor.

Research focus on HPV association and host tumor response might be helpful to understand the clinical and pathological aspects of this rare tumor.

Current series emphasises the multi centric nature of this tumor which associate with occurrence of second primary.

Conflict of interest None.

Funding None.

References

1. Ackerman LV (1948) Verrucous carcinoma of the oral cavity. *Surg* 23:670–678
2. Koch BB, Trask DK, Hoffman HT, Karnell LH, Robinson RA, Zhen W, Menck HR (2001) National survey of head and neck verrucous carcinoma. *Cancer* 92(1):110–120
3. Medina JE, Dichtel W, Luna MA (1984) Verrucous-squamous carcinomas of the oral cavity: a clinicopathologic study of 104 cases. *Arch Otolaryngol* 110(7):437
4. Walvekar RR, Chaukar DA, Deshpande MS, Pai PS, Chaturvedi P, Kakade A, D'Cruz AK (2009) Verrucous carcinoma of the oral cavity: a clinical and pathological study of 101 cases. *Oral Oncol* 45(1):47–51
5. Tornes K, Bang G, Koppang HS, Pedersen KN (1985) Oral verrucous carcinoma. *Cancer* 46(8):1855–1862
6. Lübke J, Kormann A, Adams V, Hassam SH, Grätz KW, Panizzon RG, Burg G (1996) HPV-11-and HPV-16-associated oral verrucous carcinoma. *Dermatol* 192(3):217–221
7. Fontes EA, Greenlaw RH, Rush BF, Rovin S (1969) Verrucous squamous cell carcinoma of the oral cavity. *Cancer* 23(1):152–160
8. Oliveira DT, de Moraes RV, Fiamengui Filho JF, Neto JF, Landman G, Kowalski LP (2006) Oral verrucous carcinoma: a retrospective study in São Paulo Region. Brazil. *Clin Oral Invest* 10(3):205–209
9. Bedi GC, Westra WH, Gabrielson E, Koch W, Sidransky D (1996) Multiple head and neck tumors: evidence for a common clonal origin. *Cancer Res* 56(11):2484–2487
10. Worsham MJ, Wolman SR, Carey TE, Zarbo RJ, Benninger MS, van Dyke DL (1995) Common clonal origin of synchronous primary head and neck squamous cell carcinomas: analysis by tumor karyotypes and fluorescence in situ hybridization. *Hum Pathol* 26(3):251–261