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ORIGINAL RESEARCH ARTICLE OPEN ACCESS

Oral carcinoma cuniculatum: A rare entity with diagnostic challenges. A series of 5 cases and review of literature

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Abstract – Carcinoma cuniculatum (CC) is an uncommon variant of squamous cell carcinoma (SCC). It is a low-grade tumor with an endophytic and burrowing growth pattern. The lesion initially presents as a condyloma or a hyperkeratinized patch, which eventually ulcerates and features sinuses that discharge keratinous material. To date, CC remains rare, with about 75 reported cases, and it is frequently missed or misdiagnosed. The aim of the present work is to report five cases of CC in the gingivobuccal complex and highlight its main clinicopathological diagnostic features: an exophytic cobblestone surface and a characteristic endophytic burrowing architecture, as well as to differentiate it from other closely similar lesions, including verrucous carcinoma, papillary squamous cell carcinoma, and well-differentiated conventional oral squamous cell carcinoma. An accurate diagnosis of CC requires clinicians' and pathologists' awareness of this entity, a thorough understanding of the diagnostic clinical and histopathological evidence, and the ability to differentiate it from similar lesions.

Key words: Oral carcinoma cuniculatum,, Rabbit burrows,, Verrucous carcinoma..

Introduction

Carcinoma cuniculatum (CC), also known as cuniculate carcinoma, is a rare low- grade carcinoma [1]. Arid et al. reported the first case series of CC on the plantar surface of the foot [2]. CC has been documented in other locations, including the abdominal wall, skin, and genital region [3]. However, the oral cavity was first identified as a site for CC by Flieger and Owinski [4]. Numerous synonyms have been used to describe this entity, including epithelioma cuniculatum, Buschke–Lowenstein tumor, and inverted verrucous carcinoma (VC) [5]. Regarding its unique clinical and pathological aspects, the World Health Organization (WHO) recognized CC of the oral cavity, referred to as oral carcinoma cuniculatum (OCC), as a distinct, well-differentiated subtype of oral squamous cell carcinoma (OSCC) in 2005 and 2017. OCC and VC were also considered different subtypes, although they are often confused [6]. OCC remains a rare entity that presents diagnostic challenges, with approximately 75 cases documented in the literature from 1977 to May 2021 [7]. Herein, we present five OCC cases.

Methodology

Clinical and pathology data for all cases of CC arising in the oral cavity were retrieved from the archives of the Department of Pathology at our tertiary-care oncology institute. Haematoxylin and eosin-stained slides for all cases were collected. Clinical findings and treatment details were recorded from the hospital's electronic medical records. The recorded demographic and clinical parameters included age, gender, imaging features (computerized tomography, tumor location, and size, type of resection, clinical staging, and treatment administered). The pathology features analyzed included tumor size (pT), histologic type, grade, architectural growth patterns, depth of invasion (DOI), pattern of invasion (POI), lymphovascular invasion

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Figure 1. Gross image of the tumour showing the ulceroproliferative tumour involving buccal Mucosa (blue star), lower gingivobuccal sulcus (blue cross) and mandible (blue arrow).

(LVI), perineural invasion (PNI), surgical margins, lymph node (LN) status, and pathologic TNM staging as per the AJCC, 8th edition (Figures 1–3; Tables 1 and 2).

Discussion

Carcinoma cuniculatum of the oral cavity is a rare variant of SCC as it is under-recognized among both, pathologists and oncologists, even five decades after it was first described in the head and neck region. Sun et al. in their study with 540 cases of SCC [8]. Cases are mostly reported in the sixth and seventh decades with female preponderance [9]. In our study, one case out of five was found in the 4th decade, with a male preponderance, which was also reported in other studies [10, 11].

The most frequently reported sites of origin of oral CC were the alveolus and hard palate [12]; in our study, the buccal mucosa was the most common site. The exact aetiology and causative mechanisms, as suggested by multiple studies, are long- standing (neuropathic) ulcers, trauma, tobacco, alcohol, poor oral hygiene, and human papillomavirus (HPV; types 1–4, 6, 11, and 18), along with tobacco consumption and smoking [8, 12, 13]. All our patients had a history of smoking and tobacco cessation.

The three histologic features that characterise Carcinoma cuniculatum are [14]:

1) a complex architecture with branching sinuses and keratin-filled cysts resembling the eponymous rabbit cuniculus (burrow); 2) broad and bulbous rete pegs; and 3) lack of (or minimal) cytologic atypia. The usual growth pattern of CC is predominantly an endophytic component of well-differentiated squamous cells that forms tortuous, deep sinuses and interconnected, elongated, cavernous cavities filled with abundant keratin, with a variable exophytic component. All our cases showed these distinctive keratin-filled cavities. Owing to the deeply infiltrative growth pattern in CC, these tumours are

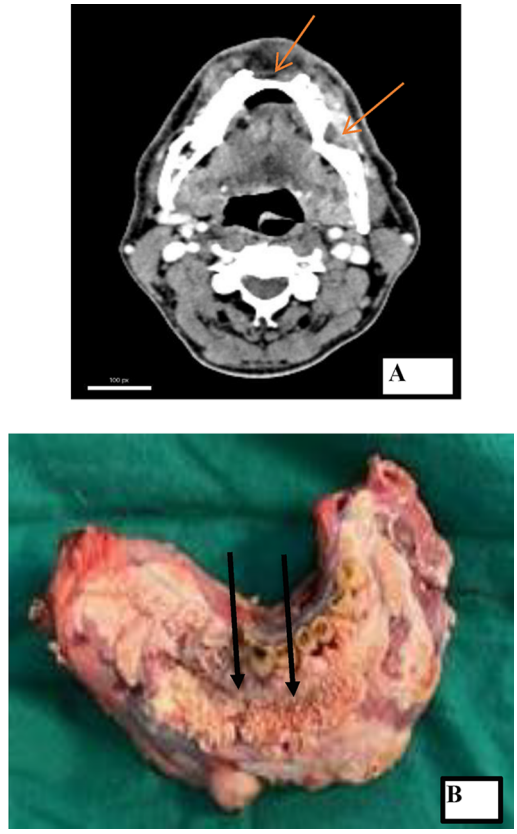

Figure 2. (A) Radiology showing bony erosion of the mandible (marked by red arrows) and (B) gross image of the tumour of the same patient showing the ulceroproliferative tumour involving lower gingivobuccal sulcus (black arrows) and mandible.

locally aggressive. Two of our cases showed bone infiltration. Intraepithelial neutrophils and a prominent cuff of lymphocytes, plasma cells, foreign-body giant cells, and microabscesses at the tumour edge are often seen. Perineural invasion and LVI are usually not a feature of oral CC. None of our cases showed LVI and PNI.

The closest differential diagnosis is Verrucous carcinoma (VC), characterised by mostly exophytic growth, formed by well-differentiated squamous cells. Branching and interconnected cyst-like sinuses filled with keratin are absent in VC, which are pathognomic of CC. Nodal metastasis is uncommon in both.

The diagnosis of CC is possible only in resected specimens in which the pathognomic architecture is seen. Lack of atypia and the tumour mostly being infiltrative, the diagnosis in a punch biopsy is often missed.

The primary modality of treatment is surgery with clear margins. RT and CT do not appear to play a significant role in CC. Lymph nodal metastases are reported in 14–24% of cases [15, 16]. Despite being locally aggressive and rare instances of metastases, the prognosis is favourable [17]. Local recurrences have been reported irrespective of free margins in 3–27% [18]. In our study, the minimum follow-up was 1 year, and only one patient showed local recurrence.

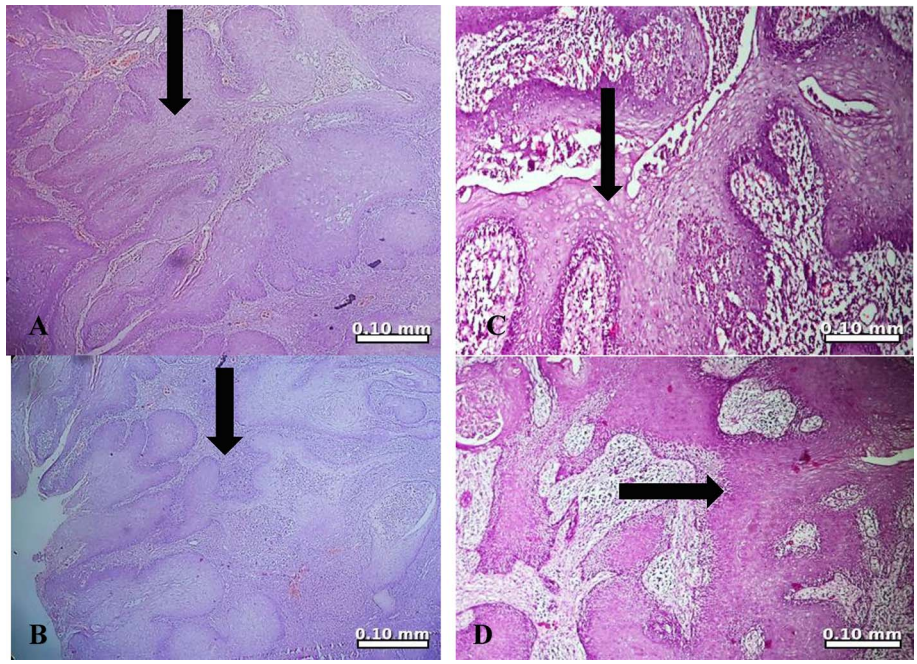

Figure 3. (A) 10× view showing proliferating well differentiated squamous epithelium (black arrow); (B) 10× view showing the burrowing nature (black arrow) of Carcinoma cuniculatum; (C) and (D): 40× view of the well differentiated squamous epithelium with no dysplasia (black arrow).

Table 1. Summary of all the five cases.

Features	Case 1	Case 2	Case 3	Case 4	Case 5
Age	60	62	46	71	72
Sex	Male	Male	Male	Female	Female
Local examination	Ulceroproliferative growth was noted in the left buccal mucosa reaching the left lower gingivobuccal sulcus and retromolar trigone measuring 2.5 × 2.5 cm	Ulcerative growth in the right buccal mucosa upto retromolar trigone.	Ulceroproliferative growth in left buccal mucosa and lower gingivobuccal sulcus	Ulceroproliferative growth in right buccal mucosa	Ulcerated lesion noted over right LGBS and alveolus.
CT findings	Lesion in the left buccal mucosa measuring 12.4 mm with no bony erosions	Enhancing thickening 31 × 22 × 9 mm in buccal mucosa, reaching up to retromolar trigone with superficial erosion of right mandible.	Tumour measuring 2.3 × 2.2 cm lesion involving the left LGBS with RMT involvement and erosion of left hemimandible.	3.2 × 2 cm lesion involving the right buccal mucosa extending to upper GBS and erosion of right upper alveolus.	3.6 × 2.5 cm lesion involving right lower GBS and alveolus with right mandibular bony involvement.
Punch biopsy	Well-differentiated squamous cell carcinoma	Well differentiated squamous cell carcinoma	Well-differentiated squamous cell carcinoma	Moderately differentiated squamous cell carcinoma	Moderately differentiated squamous cell carcinoma
cTNM	cT2N0	cT4aN0	cT2N0	cT4aN0	cT4aN0

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Table 1. (Continued)

Features	Case 1	Case 2	Case 3	Case 4	Case 5
Management of the primary lesion- Upfront surgery with lymphadenetomy for all the cases	Left marginal mandibulectomy with left selective neck dissection (I-III) and submental flap repair	Wide Local excision + Segmental Mandibulectomy and MRND type II and PMMC flap repair	Wide local excision with segmental mandibulectomy with Selective neck dissection (I-III) With primary repair.	Infrastructure maxillectomy with extended Supraomohyoid neck dissection (I-IV) with obturator placement	Wide Local Excision + Rt Segmental Mandibulectomy +Rt upper Alveolectomy with selective neck dissection (I-III).
Final HPE	Carcinoma cuniculatum	Carcinoma cuniculatum	Carcinoma cuniculatum	Carcinoma cuniculatum	Carcinoma cuniculatum
Tumour size	3 × 2 × 0.8 cm	3.1 × 2.2 × 0.9 cm	3 × 2 × 1.5 cm	4 × 2 × 1 cm	3 × 3 × 1.8 cm
Site	Buccal mucosa	Buccal mucosa	Buccal mucosa	Upper gingivobuccal sulcus, alveolus	RMT, Lower and upper GBS, upper alveolus
DOI	0.7	1.7	1.1	0.5	1.2
LVI/PNI	–/–	–/–	–/–	–/–	–/–
WPOI	4	4	3	3	4
Margins	Negative	Negative	Negative	Negative	Negative
Underlying bone	Uninvolved	Involved	Uninvolved	Involved	Involved
Neck lymph nodes	0/31	0/17	0/19	0/33	0/25
pTNM	pT2N0	pT4aN0	pT3N0	pT4aN0	pT4aN0
Head and neck DMG* decision	Observation	Adjuvant RT	Observation	Adjuvant RT	Adjuvant RT
Follow-up (12–18 months)	Doing well No recurrence	Doing well No recurrence	Doing well No recurrence	Patient developed local recurrence. Started on oral metronomic therapy	Doing well No recurrence

*DMG – Disease management group.

Table 2. Summary of literature on oral carcinoma cuniculatum [6].

Author	Sex	Age	Location	Bone involvement	Initial diagnosis	Risk factors	Recurrence	Mets
Flieger et al. 1977	M	50	Alveolus	Yes	Osteomyelitis	N/A	N/A	N0M0
	M	60	Alveolus	Yes	Tuberculosis	Poor oral hygiene	N/A	N0M1
	M	9	Alveolus	Yes	N/A	N/A	N/A	N0M0
	F	69	Hard palate	Yes	N/A	N/A	N/A	N0M0
Kuffer et al. 1984	M	43	Alveolus	N/A	N/A	N/A	N/A	–
	M	68	Alveolus	N/A	N/A	N/A	N/A	–
	M	16	RMT	N/A	N/A	N/A	N/A	–
	F	44	Tongue	N/A	N/A	N/A	N/A	–
	F	44	Epiglottis	N/A	N/A	N/A	N/A	–
Kahn et al. 1991	M	62	Alveolus	Yes	Cyst		Yes	N0M0
	F	49	Alveolo- lingual groove	Yes	WD- EC	Alcohol- smoking	No	N0M0
	M	52	Floor of mouth	Yes	WD-EC	N/A	No	N0M0
	F	54	Alveolo- lingual groove	Yes	None	N/A	No	N0M0
Delahaye et al. 1994	M	51	RMT	N/A	WD-EC	Alcohol- smoking	Yes	N1M0
	M	55	Tongue + floor of mouth	N/A	VC	N/A	Yes	N0M0
	M	31	Hard palate	No	WD-EC	N/A	No	N0M0
	M	63	Larynx	N/A	N/A	N/A	N/A	N0M0
	M	52	Cheek mucosa	N/A	N/A	Alcohol- smoking	N/A	N0M0
Huault et al. 1998	F	55	Alveolus	Yes	Papilloma	Tooth extraction	No	N1M0
Allon et al. 2002	M	56	Alveolus	Yes	None	N/A	No	N0M0
Gallo et al. 2005	M	47	Lips + cheek	Yes	None	N/A	Yes	–
Raguse et al. 2006	F	81	Mandibular symphysis	Yes	N/A	N/A	N/A	–
Puxeddu et al. 2008	M	72	Larynx	N/A	Pseudo- epithelial hyperplasia	N/A	N/A	N0M0
Kruse et al. 2009	F	74	Maxilla	Yes	EC	None	No	N0M0
Hutton et al. 2010	F	7	Maxilla	Yes	Cyst	None	No	N0M0

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Table 2. (Continued)

Author	Sex	Age	Location	Bone involvement	Initial diagnosis	Risk factors	Recurrence	Mets
Pons et al. 2010	M	72	Mandible	Yes	Abscess	N/A	No	N0M0
	M	82	Mandible	Yes	Cyst	N/A	No	N0M0
	M	43	RMT	Yes	Cyst	N/A	No	N0M0
Sun et al. 2011	7 M 8F	67	8 tongue 6 mandible 1 vestibule	5 Yes 10 No				3N1M0 12N0M0
Thavaraj et al. 2011	M	61	Tongue	No	N/A	N/A	No	
Suzuki et al. 2012	M	68	Alveolus	Yes	Osteomyelitis	Alcohol-smoking	Yes	N0M0
Fonseca et al. 2013	F	62	Mandibule	Yes	super-infected cyst	None	No	N0M0
	F	47	Alveolus	Yes	Osteomyelitis	None	No	–
Padilla et al. 2014	M	65	Alveolus	N/A	Hyperkeratosis	N/A	N/A	–
	F	38	Alveolus	No	Hyperplakia	None	NA	–
	M	72	Alveolus	No	N/A	None	No	–
	F	81	Alveolus	No	N/A	None	No	–
	F	65	Alveolus	N/A	Lichen planus	None	N/A	–
	M	79	Alveolus	Yes	N/A	Alcohol – smoking	No	–
	F	88	Alveolus	No	N/A	None	No	–
	F	75	Alveolus	No	Dysplasia	Smoking	No	–
	F	69	Alveolus	No	N/A	None	No	–
	F	85	Alveolus	No	N/A	None	N/A	–
Shay et al. 2015	M	58	Mandible	Yes	Odontogenic Keratocyst	None	Yes	N0M0
Shapiro et al. 2015	F	71	Para- symphysis	Yes	Leucoplakia	Smoking	N/A	N0M0
Datar et al. 2017	F	58	Right gingiva	Yes	SCC	No	N/A	N0M0
Thibouw et al. 2018	M	57	Lower lip	Yes	scar-like inflammatory suspected mycetoma	Smoking	No	
Zhang et al. 2018	M	39	Lower gingiva	Yes	SCC	Smoker	No	N1M0
Ajith et al. 2018	M	71	Tongue	Yes	Multiple inconclusive biopsies	No	Yes	N1M0
	M	63	Mandible	Yes	Odontogenic keratocyst	No	Yes	N0M0
Broly et al. 2019	M	78	Dental pain in second mandibular region	Yes	Odontogenic infection	Smoking and Alcohol	No	N0M0
Sivapathasundharam et al. 2019	F	47	Lower tooth	Erosion	NA	None	No	–
Barrett et al 2020	M	78	Mandible	Yes	N/A	N/A	N/A	N0M0
	M	71	Mandible	Yes	Verrucous leukoplakia	N/A	N/A	N0M0
	F	94	Mandible	Yes	N/A	N/A	N/A	N0M0
	M	69	Mandible	Yes	N/A	N/A	N/A	N0M0
Janardhanan et al. 2021	M	63	Right lower jaw	Yes	Odontogenic kerato cyst	N/A	Yes	N0M0
Yadav et al. 2021	M	41	Tongue	No	WDSCC	Tobacco	No	N0M0
	M	37	Tongue	No	Hyperplastic squamous epithelium	Tobacco, betel quid	Yes	N1M0
	F	45	Palate	No	WD SCC	Betel-leaf	No	N0M0
	M	45	Right lower GBS	Yes	Hyperplastic squamous epithelium	Smoking; alcohol	No	N1M0
	M	77	Left upper GBS	No	WDSCC	Tobacco	No	N0M0
	M	25	Right buccal mucosa	No	Atypical squamous	Tobacco	No	N0M0
Malhotra et al. (present study)	M	60	Left Buccal Mucosa	No	WDSCC	Tobacoo	No	N0M0
	M	62	Right Buccal Mucosa	Yes	WDSCC	Tobacoo	No	N0M0
	M	46	Left Buccal Mucosa	No	WDSCC	Smoker	No	N0M0
	F	71	Upper GBS	Yes	MDSCC	Betel leaf	No	N0M0
	F	72	Lower GBS and RMT	Yes	MDSCC	Betel leaf	Yes	N0M0

Conclusion

Although rare, awareness of OCC among pathologists, oncosurgeons, and oncologists can be helpful in the recognition and better management of these cases. More studies with longer follow-up are necessary to determine the metastatic potential and recurrence.

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Conflicts of interest

The authors declare that they have no conflicts of interest related to this study.

Data availability statement

The data supporting the findings of this study are available from the corresponding author upon reasonable request. The data are not publicly available due to institutional policies and patient confidentiality.

Author contribution statement

M.M contributed to study conception, surgical management, data collection, and manuscript drafting. A.S contributed to histopathological evaluation, manuscript editing, and the article submission process. S.B. contributed to clinical management and review of the manuscript. A.K.D., T.R., R.B., S.A., and L.K. contributed to the analysis, and critical revision of the manuscript. All authors read and approved the final manuscript.

Ethics approval

This study was approved by the Institutional Ethics Committee of Dr B. Borooah Cancer Institute, Guwahati. Given the retrospective nature of the study and use of anonymized patient data, the requirement for informed consent was waived.

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