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Case Report

Dentistry Section

Oral Carcinoma Cuniculatum: A New Entity in the Clinicopathological Spectrum of Oral Squamous Cell Carcinoma

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ABSTRACT

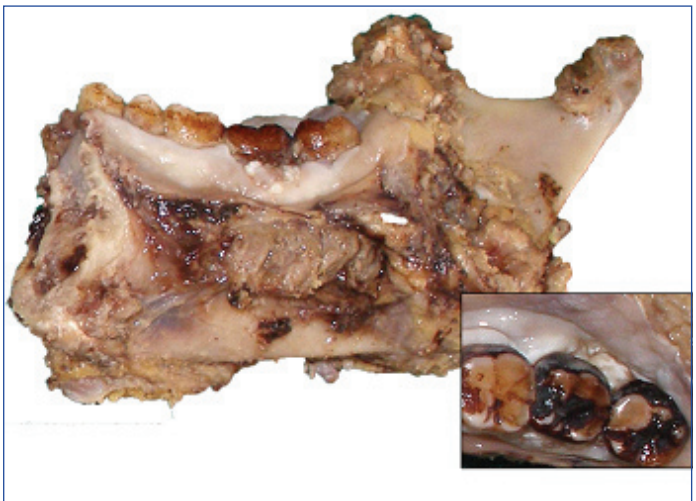
Carcinoma cuniculatum is principally recognized as a variant of carcinoma involving foot. The World Health Organization (WHO) recognizes Oral Carcinoma Cuniculatum (OCC) as a distinct and rare clinicopathological variant of Oral Squamous Cell Carcinoma (OSCC). OCC is confused clinically and histologically with Verrucous Carcinoma (VC) and is often misdiagnosed as either VC or OSCC. To best of our knowledge, till date, only 50 cases of this tumour have been reported in oral cavity (including the present case) and only limited number of cases have been reported from Indian subcontinent. Pathognomonic feature of OCC is proliferation of stratified squamous epithelium and its infiltration into underlying stroma forming a complex pattern of keratin cores and keratin filled crypts. These complex crypts give it a likeness of rabbit burrow hence, the name cuniculatum (cuniculatus='rabbit warren'). The report aims to present a case of OCC of mandibular gingiva, discuss its diagnostic features and highlight its differences from VC and OSCC.

Keywords: Differential diagnosis, Rabbit burrows, Verrucous carcinoma

CASE REPORT

A 58-year-old female patient presented with a complaint of non healing ulcer present on right mandibular gingiva since three months. The patient had visited a private dentist who performed incisional biopsy of the lesion and the histopathological report suggested well differentiated OSCC. After receiving this report the patient was guided to our institute. A thorough history and clinical information was recorded in the institute. The patient did not disclose any habit history. Oral examination revealed an ulcerated, reddish white, pebbly growth on the buccal and lingual aspect of right mandibular second molar. Panoramic radiograph of the patient showed irregular radiolucent lesion involving the alveolar bone around right mandibular second molar. With clinical presentation, radiographic evidence of bone invasion and histopathological report of OSCC, treatment planned was, hemimandibulectomy with ipsilateral Type II modified neck dissection.

The resected specimen [Table/Fig-1] along with ipsilateral Type II modified neck dissection was sent for histopathological diagnosis.

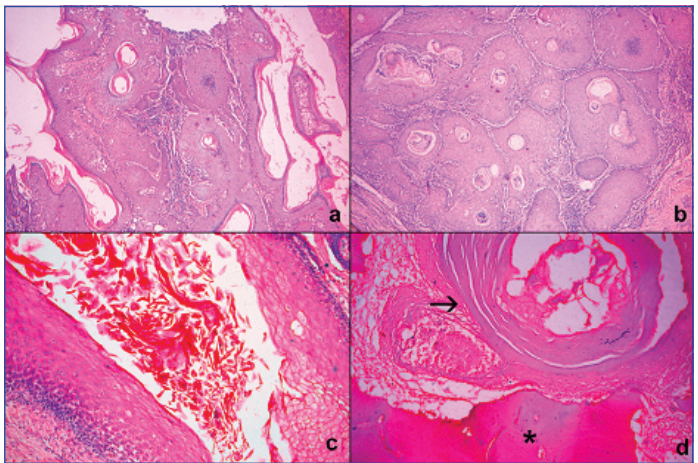


[Table/Fig-1]: Lingual view of resected hemimandibulectomy specimen is noted showing reddish white pebbly growth on the buccal and the lingual surface of right mandibular second molar, the inset shows occlusal view.

Microscopically the lesion revealed a well differentiated stratified squamous epithelium forming multiple, complex, branching keratin filled crypts [Table/Fig-2a-c]. These crypts showed the characteristic burrowing pattern. The tumour cells in the crypts showed mild cytological atypia and few mitotic figures limited to basal and parabasal layers. The tumour islands were seen invading the bony trabaculae [Table/Fig-2d]. A diagnosis of OCC was made based on the above mentioned observations. The tumour margins were clear of the tumour tissue and none of the regional lymph nodes demonstrated metastasis. After two years of postoperative follow up, the patient continues to be clinically and radiographically disease free.

DISCUSSION

OCC is a rare variant of OSCC [1,2]. Carcinoma cuniculatum was first described in the foot by Arid I et al., in 1954 [3]. But OCC was first described in oral cavity by Fliegar S and Owanski T in 1977 [4]. The diagnostic feature of OCC is well differentiated epithelial cells which



[Table/Fig-2a-d]: Photomicrographs showing: a) Deeply located branching crypts and keratin filled debris surrounded by squamous epithelium which resemble rabbit burrows; (H&E, 4X); b) Invasive front of cuniculatum (H&E, 4X); c) Keratin crypts surrounded by well differentiated squamous epithelium showing minimal atypia (H&E, 10X); d) Photomicrograph of decalcified section showing tumour islands invading in bone, arrow points the tumour island and * indicates the bone trabaculae (H&E, 10X).

Authors	Number of cases	Age/ Gender	Site	Preoperative Diagnosis/Initial Diagnosis
Fliegar S and Owanski T [4]	4	50/M	Maxillary molar and sinus	Osteomyelitis
		60/M	Maxillary molar region	Tuberculosis
		9/M	Maxillary premolar region	Not stated
		69/F	Hard palate	Not stated
Kahn JL et al., [13]	3	62/M	Maxillary alveolus and sinus	Cystic lesion
		49/M	Submandibular space	Not stated
		52/M	Anterior floor of the mouth	Not stated
Delahaye JF et al., [14]	5	51/M	Retromolar trigone	Squamous cell carcinoma
		55/M	Tonsil, floor of the mouth	Verrucous carcinoma
		63/M	Subglottic larynx	Not stated
		31/M	Hard palate	Not stated
		52/M	Buccal mucosa	Not stated
Huault M [15]	1	55/M	Mandibular alveolus	Hyperkeratotic papilloma
Allon D [1]	1	56/M	Maxillary gingiva	Giant cell lesion /Periodontal disease/ Malignancy
Raguse JD [16]	1	81/F	Mandible	Osteomyelitis
Kruse AL and Graetz KW [17]	1	74/F	Maxillary alveolus	Squamous cell carcinoma
Hutton A [18]	1	7/M	Maxilla	Abscess
Pons Y et al., [9]	3	72/M	Mandibular molar region	Inflammatory granuloma
		82/M	Mandibular molar region	Not stated
		43/M	Mandibular retromolar region	Keratocyst
Thavaraj S et al., [5]	1	61/M	Tongue	Not stated
Sun Y et al., [7]	15	Age- 44-92 Gender: 7 Male, 8 Female	Tongue-8, Mandible-6, Oral vestibule-1	Not stated
Fonseca FP et al., [10]	2	62/M	Anterior mandible	Infected orthokeratinized keratocyst
Padilla RJ and Murrah VA, [6]	10	47/F	Maxillary gingiva	Osteomyelitis
		65/M	Mandibular gingiva	Erythroleukoplakia
		38/F	Mandibular gingiva	Benign proliferation
		72/M	Mandibular gingiva	Not stated
		81/F	Maxillary anterior region	Not stated
		67/F	Mandibular gingiva and buccal mucosa	Lichen planus/ Carcinoma
		79/M	Mandibular gingiva, vestibule	Not stated
		88/F	Maxillary ridge	Not stated
		75/F	Mandibular gingiva/ridge and buccal mucosa	Hyperkeratosis
		69/F	Mandibular alveolar region	Not stated
		85/F	Mandibular gingiva	Not stated
Shakil M et al., [11]	1	63/F	Not stated	Not stated
Present case	1	58/F	Mandibular gingiva	Oral squamous cell carcinoma
	Total= 50			

[Table/Fig-3]: Overview of previously published cases of oral carcinoma cuniculatum.

	Carcinoma Cuniculatum	Verrucous Carcinoma
Aetiological Factors [1]	Alcohol, smoking	Snuff and tobacco chewing
Age [1,4-18]	7-92 years	50-80 years
Clinical Features [1,6,10]	Slow growing locally destructive; Blunt papillary/cobblestone surface; Infiltrating	Slow laterally growing; Broad warty, cauliflower-like growth; Exophytic
Radiological Features [10]	Deep invasion into the bone	Superficial bone erosion
Histopathological Features [1,6,10]	Well differentiated neoplastic cells with bland cytology and minimal cellular atypia; Chiefly endophytic growth pattern; Keratin filled crypts showing complex branching pattern are the hallmark of the tumour	Well differentiated neoplastic cells with bland cytology and minimal cellular atypia; Principally exophytic, and endophytic growth pattern; Vertical church-spire like keratinization and parakeratin plugging are the hallmark of the tumour
Immunohistochemical Findings [11]	Lesser expression of p53, Ki67 and p63; Strong expression of E cadherin, Integrin α6, Laminin 5γ2	Strong expression of p53, Ki67 and p63; Negative for E cadherin, Integrin α6 and less expression of Laminin 5γ2
Prognosis [7]	Better than OSCC, not good when compared to VC	Better than OCC and OSCC

[Table/Fig-4]: Differential diagnosis between carcinoma cuniculatum and verrucous carcinoma.

lack cytological atypia, exhibiting blunt papillary/pebbly surface and keratin filled crypts extending deep in the connective tissue [5,6]. These keratin filled crypts impart classic 'rabbit burrow' pattern to OCC. It has been noted that many pathologists are unacquainted with the lesion and the diagnostic criteria is not defined which has resulted in under-reporting of OCC.

OCC has been identified with a plethora of synonyms including epithelioma cuniculatum, Busche-Lowenstein tumour and inverted verrucous carcinoma [2,6]. The array of synonyms, failure to recognize it as a distinctive variant of OSCC and general lack of awareness about the lesion added to the rarity of the tumour and are accountable for the fewer number of published cases of OCC. Owing to this the frequency of the tumour has been underestimated [1]. The causative factors like tobacco, alcohol, trauma and Human Papillomavirus (HPV) have been indicated as aetiologic agents [1,5-7]. The presence of HPV DNA was demonstrated in cutaneous carcinoma but the association of HPV and OCC has not been proved till date [1,5,6]. In a recent case series, OCC which had preceding premalignant lesion/condition has been reported, indicating a multistep malignant transformation of premalignant lesion/condition to OCC [8].

In the cases of OCC reported till date, the most common site affected was mandibular gingiva [1,4-18]. The clinicopathological profile of cases of OCC reported till date is depicted in [Table/Fig-3], A wide age range of 7-92 years has been reported and slight male preponderance is noted [Table/Fig-3]. But in two recent case series of OCC slight female predominance was observed [6,7]. OCC presents as sessile white to pink slightly pebbly/papillary surface. Bone invasion is hallmark of OCC which was exemplified in the present case. The bone erosion was noted radiographically and the tumour islands were noted histopathologically.

Histologically, OCC is characterized by presence of keratin filled crypts which are lined by stratified squamous epithelium showing minimal cellular atypia [6]. Histological differential diagnoses include well differentiated OSCC and VC [1,6]. Burrowing pattern, keratin filled crypts, lack of obvious cellular atypia and bone invasion differentiate OCC from well differentiated OSCC [2]. Correlation with clinical and radiographic features is essential for diagnosis.

OCC and VC demonstrate a peculiar overlap in their histological and clinical presentation, but they demonstrate a different biological course [1,2,6]. Hence, differentiation of the two lesions is essential [Table/Fig-4]. Both the lesions present with exophytic and endophytic components. They exhibit minimal cytological atypia, well differentiated tumour cells and excessive keratin production. These similarities are the reason for OCC being misdiagnosed as VC. The exophytic component of OCC has a blunt papillary/cobblestone appearance whereas, VC has vertical fronds or 'church spire-like' structure [6,7]. Epithelial clefting and parakeratin plugging are hallmarks of VC whereas, OCC shows complex branching of keratin filled crypts. Pathognomonic feature of OCC is invasive epithelial component arranged in the form of keratin filled channels and cores which aids in diagnosing OCC [6,10]. VC has predominantly exophytic component but more restrained pushing front and it is limited to lamina propria [1]. On the other hand OCC burrows deep into underlying muscles and bone [1,6,8]. These features are evident in the present case. OCC is locally aggressive and distant metastasis is hardly reported [1].

The burrowing pattern has been acknowledged as a hallmark of this lesion. A recent study has reported higher expression of E-cadherin, Integrin $\alpha 6$ and Laminin $5\gamma 2$ in OCC than in OSCC and VC, which may be the reason for the peculiar burrowing pattern of this entity [12]. Laminin $5\gamma 2$ is associated with invasion, its strong expression in OCC may be a sign of invasion and deep burrows of the lesion [12]. Accumulation of E cadherin (which is responsible for cell-cell adhesion) in OCC is presumed to be a cause of branching crypt construction [12].

Sun Y et al., also found lesser expression of Ki-67, p53 and p63 in OCC as compared OSCC and VC, suggesting that OCC is less aggressive, thus proving its known biological behaviour immunohistochemically [12]. Prognosis of OCC is reported to be good despite of evidence of metastasis. These findings support that the biological behaviour of OCC is different from VC and OSCC. But whether its prognosis is better than VC is still to be understood.

CONCLUSION

We reported a case of OCC, it is important to differentiate it from VC and OSCC and aspire to advance awareness of this distinct entity amongst pathologists. To reach to a correct diagnosis; deep biopsy, clinicopathological correlation is necessary and adequate sampling is essential. It is advisable that the clinicians furnish pathologists with clinical photograph to facilitate clinical correlation and provide generous biopsy from multiple sites if OCC is suspected and the pathologists are encouraged to procure extensive sectioning of the surgical specimen to aid in diagnosis. We also stress the need of establishing diagnostic criteria for OCC to distinguish it from VC.

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