CASE REPORT

A Rare Case of Carcinoma Cuniculatum Involving the Larynx in Association with a Saccular Cyst

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Abstract Carcinoma cuniculatum (CC), a rare, well-differentiated variant of squamous cell carcinoma, is uncommon in head and neck sites but when it does occur is most common in the oral cavity. Here we report a rare case of CC involving the larynx. A 49-year-old man presented with 10 months of worsening hoarseness and, despite multiple biopsies, no diagnosis of malignancy could be established. Eventual partial excision of the lesion and histologic review of prior specimens confirmed the diagnosis of CC. Focally, a transition to respiratory epithelium indicated the presence of an associated saccular cyst. Total laryngectomy was performed and 6 months later the patient is free of disease. Only two prior cases of CC have been reported in the larynx. Diagnosis of CC is challenging given the low grade histologic features and awareness of this entity for both treating physicians and the pathologist is important to reach a diagnosis of malignancy. This case highlights the challenges in diagnosis of CC, especially in unusual locations and when associated with other lesions such as a saccular cyst. Awareness of this rare tumor type combined with close communication between treating clinicians, radiologists and pathologists should allow earlier diagnosis and treatment.

Keywords Larynx · Carcinoma cuniculatum · Verrucous carcinoma · Saccular cyst

Introduction

Carcinoma cuniculatum (CC) is a rare, well differentiated variant of squamous cell carcinoma first described by Aird et al. [1] on the sole of the foot, though known to occur at other sites even at the time of this initial description. Cuniculatum, derived from the Latin, references the deep, complex pattern of invasion by keratinizing squamous epithelium lined channels resembling rabbit burrows. Cystic dilation of these channels is not uncommon. Like verrucous carcinoma (VC), CC tends to be well differentiated with low grade cytonuclear features, making diagnosis difficult to establish on small biopsy samples, often leading to delays in treatment [2]. Although similarities exist between CC and VC, and the literature occasionally uses the terms interchangeably, there are some differences, and the 2005 edition of the WHO Pathology and Genetics of Head and Neck Tumours includes CC as a separate variant of squamous cell carcinoma [3]. The etiology of CC is not clear but some of the proposed risks include chronic trauma, Human Papilloma-virus infection, alcohol, and tobacco [4, 5].

Case Report

A 49-year-old man with a reported history of smoking 2–3 cigarettes daily presented with 10 months of hoarseness and a left vocal fold mass. An initial biopsy demonstrated chronic inflammation, hyperplasia and parakeratosis, and a partial excision of the mass showed a laryngeal nodule with granulation tissue and reactive inflamed squamous

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epithelium. Two months later, nasopharyngolaryngoscopy revealed an erythematous, irregular mass with surface leukoplakia involving the true and false vocal folds. The mass subsequently evolved over the course of a year into an exophytic growth affecting the bilateral glottic larynx, and extending to the subglottis (Fig. 1).

The patient's course was also complicated by multiple laryngeal abscesses requiring incision and drainage, eventually leading to a chronically draining external neck wound. Imaging demonstrated multiloculated, phlegmonous collections varying over time with a persistently enlarging anterior neck mass, ultimately circumferentially involving the hypopharynx and larynx with thyroid cartilage destruction and skin ulceration. Multiple laryngeal biopsies during this course were initially reported as negative for malignancy. The patient then underwent a wide local excision and debridement of the neck mass.

Sections of this mass showed complex, branching networks of mostly bland, keratinizing squamous epithelium with cyst formation 'burrowing' through soft tissue (Fig. 2). Additionally, there were areas of the tumor with a more prominent papillary growth pattern (Fig. 3). These broad papillae were lined by bland squamous epithelium which combined with the architecture made it more challenging to arrive at a diagnosis of invasive squamous cell carcinoma. While mostly bland, a few foci demonstrated cytologic atypia, and small angulated nests in a fibrocellular stroma (Fig. 4). Interestingly a transition to ciliated pseudo stratified columnar epithelium was noted in tumor cysts in the neck soft tissue (Fig. 5). On re-review, the laryngeal biopsies also demonstrated scattered areas with mild to moderate cytologic atypia and focal infiltration of the stroma. Overall the findings were diagnostic of a well-differentiated squamous cell carcinoma and specifically of the cuniculatum variant.

Fig. 1 Laryngoscopic strobe image of the patient's laryngeal mass involving the bilateral larynx prior to total laryngectomy

Fig. 2 Excision of neck mass (hematoxylin and eosin, $\times 40$). Histologic image of the tumor showing burrow-like channels of bland squamous epithelium. Centrally, these channels showed cystic dilation and often contained keratin debris

Fig. 3 Area of papillary growth pattern (hematoxylin and eosin, $\times 40$). Focally the tumor showed areas of prominent papillary growth with a bland squamous lining further complicating the diagnosis of an invasive malignancy

Total laryngectomy with bilateral neck dissection was performed. Gross and histologic examination of this specimen confirmed the diagnosis of CC and an associated saccular cyst. Carcinoma extended to the preepiglottic space and soft tissues of the anterior neck with formation of a cutaneous fistula. All margins and lymph nodes were negative for malignancy. Six months after surgery the patient is recovering and is free of carcinoma.

Discussion

Although the sole of the foot still appears to be the most common site [6], CC has also been reported in other

Fig. 4 Focal atypia and angulated tumor nests (hematoxylin and eosin, $\times 40$). Focally the tumor showed areas of increased atypia and infiltrative, angulated tumor nests more in keeping with a conventional squamous cell carcinoma

cutaneous sites including the penis [7] and hand [8]. Additionally, an increasing number of reports describe CC involving head and neck sites, predominantly the oral cavity [2, 4, 9–11, 13–22]. Table 1 summarizes all reports of CC occurring in the head and neck which could be identified. Only two cases of CC have been previously reported in the larynx, both showing locally aggressive disease but a favorable prognosis after surgery. One was a 72-year-old man who interestingly presented similarly to our patient with multiple ‘abscesses’ of the preepiglottic and prelaryngeal soft tissue, but also extensive thyroid cartilage involvement; this patient was disease free 70 months after surgery [5]. The other was a 63-year-old man with extensive involvement of the right hemilarynx with subglottic extension with no evidence of disease 42 months following surgery [9].

The current case also appears to be the first known to involve a saccular cyst as evinced histologically by the transition of some tumor cysts in the neck soft tissue to respiratory-type epithelium and subsequently confirmed on resection. Saccular cysts (laryngoceles) are more frequently present in patients with squamous cell carcinoma for unknown reason, possibly a result of a one-way valve mechanism due to intermittent tumor obstruction. However, only about half of these are actually ipsilateral to the tumor and even rarer still is colonization of the saccular cyst by tumor [23]. All documented cases of carcinoma involving saccular cyst are of the conventional type of squamous cell carcinoma, and this is the first variant morphology to be documented with a saccular cyst. We postulate that involvement of this saccular cyst facilitated extension of this tumor throughout the neck in this case.

As with other well-differentiated morphologic variants of squamous cell carcinoma, this case highlights the aforementioned challenge in diagnosing CC on biopsy since the diagnosis was initially not apparent on the series of biopsies and small excisions over the course of a year. Small tissue size made it difficult to establish invasion, and unlike conventional squamous cell carcinoma, cytonuclear atypia is more subtle in CC. Thus, aside from familiarity with the morphologic features of this variant, correlation with clinical and imaging characteristics is important to even raise the possibility of CC, and a more sizeable excision is usually required to establish the diagnosis.

Once a diagnosis of carcinoma is established, the differential diagnosis for CC includes VC and a subset of papillary/exophytic squamous cell carcinomas. While CC and VC are sometimes used interchangeably, strictly speaking, the pattern of invasion in VC consists of broad, bulbous rete/tumor nests, unlike the arborizing often cystic

Fig. 5 Laryngectomy showing associated saccular cyst. **a** Sections of the laryngectomy had large cystic spaces with bland squamous lining and keratin debris. Focally a transition to respiratory epithelium was seen in the lower aspect indicating the presence of an associated saccular cyst (hematoxylin and eosin, $\times 40$). **b** Higher power view

showing the focal transition from well differentiated squamous cell carcinoma to respiratory type epithelium. Here the respiratory epithelium demonstrated squamous metaplasia but retained several goblet cells (hematoxylin and eosin, $\times 100$)

Table 1 Reported cases of carcinoma cuniculatum of the head and neck

References	Case	Site	Age (years)/sex	Notes
Flieger and Owínski [10]	1	Maxillary molar region, sinus	50/M	
	2	Maxillary molar region	60/M	Lung metastasis
	3	Maxillary premolar region	9/M	
	4	Hard palate	69/F	
Kahn et al. [11]	5	Maxillary alveolus, sinus	62/M	
	6	Submandibular space	49/F	Smoker
	7	Anterior floor of mouth	52/M	
	8	Mandibular molar region	54/F	
Delahaye et al. [9]	9	Larynx, subglottic	63/M	
	10	Retromolar trigone	51/M	Smoker
	11	Tonsil, floor of mouth	55/M	
	12	Hard palate	31/M	
	13	Buccal mucosa	52/M	Smoker, nodal metastasis
Szmeja et al. [12]	14	Nasal cavity and paranasal sinuses		
Huault et al. [13]	15	Mandibular alveolus	55/F	Nodal metastasis
Allon et al. [14]	16	Maxillary gingiva	56/M	Smoker
Gassler et al. [15]	17	Buccal mucosa		
Raguse et al. [16]	18	Mandible	81/F	
Puxeddu et al. [5]	19	Larynx	72/M	Smoker
Kruse and Graetz [17]	20	Anterior maxilla	74/F	
Hutton et al. [18]	21	Anterior maxillary gingiva	7/F	
Pons et al. [2]	22	Posterior mandibular molar region	72/M	
	23	Anterior mandible	82/M	
	24	Mandibular retromolar region	43/M	
	25–39	Tongue ×8	44–92 (mean 67)	Seven smokers, three with nodal metastasis
		Oral vestibul ×1	M ×7, F ×8	One with lung metastasis
		Mandible ×6		
Suzuki et al. [19]	40	Mandibular gingiva	68/M	Smoker
Thavaraj et al. [20]	41	Oral tongue	61/M	
Fonseca et al. [21]	42	Anterior mandible	62/F	
	43	Maxilla	47/F	
Goh et al. [22]	44	Tongue	62/M	
Current case	45	Larynx involving saccular cyst	49/M	Smoker

Bold values represent previously reported cases of carcinoma cuniculatum of the larynx

tumor channels of CC. Unlike CC, VC classically demonstrates sharp spire-like exophytic projections imparting a ‘warty’ appearance. Furthermore, while cytonuclear atypia, and foci of angulated infiltrative tumor nests are definitionally absent in pure VC, these findings can be noted focally in CC. The exophytic component of CC may resemble a well differentiated papillary/exophytic squamous cell carcinoma; however, the latter does not have much of an infiltrative endophytic component, and its exophytic component is more arborizing.

Once the diagnosis is established, CC has a good prognosis. While the natural course may consist of locally destructive

growth, lymph node metastases are rare [4, 5, 9, 13]. In this case the bilateral neck dissection was negative for metastatic carcinoma. However, CC is also reported to occasionally to progress to a more conventional squamous cell carcinoma morphology [4]. Surgical resection is the mainstay of treatment, and there is likely no role for adjuvant radiotherapy [5, 9].

Conclusions

In summary, CC is a well differentiated and rare squamous cell carcinoma variant that poses considerable diagnostic

challenges on biopsy. These can be overcome by communication between the surgeon, radiologist, and pathologist and more extensive tissue sampling. This case also demonstrates the novel finding of an associated saccular cyst which may have provided an avenue for extensive spread in the neck.

Conflict of interest None.

References

1. Aird I, Johnson HD, Lennox B, Stansfeld AG. Epithelioma cuniculatum: a variety of squamous carcinoma peculiar to the foot. *Br J Surg*. 1954;42:245–50.
2. Pons Y, Kerrary S, Cox A, et al. Mandibular cuniculatum carcinoma: apropos of 3 cases and literature review. *Head Neck*. 2012;34:291–5.
3. Barnes E, Everson JW, Reichart P, Sidransky D. Pathology and genetics of head and neck tumours. World Health Organization classification of tumours. Lyon: IARC Press; 2005.
4. Sun Y, Kuyama K, Burkhardt A, Yamamoto H. Clinicopathological evaluation of carcinoma cuniculatum: a variant of oral squamous cell carcinoma. *J Oral Pathol Med*. 2012;41:303–8.
5. Puxeddu R, Cocco D, Parodo G, Mallarini G, Medda M, Brennan PA. Carcinoma cuniculatum of the larynx: a rare clinicopathological entity. *J Laryngol Otol*. 2008;122:1118–23.
6. Kao GF, Graham JH, Helwig EB. Carcinoma cuniculatum (verrucous carcinoma of the skin): a clinicopathologic study of 46 cases with ultrastructural observations. *Cancer*. 1982;49:2395–403.
7. Barreto JE, Velazquez EF, Ayala E, Torres J, Cubilla AL. Carcinoma cuniculatum: a distinctive variant of penile squamous cell carcinoma: report of 7 cases. *Am J Surg Pathol*. 2007;31:71–5.
8. Wastiaux H, Dreno B. Recurrent cuniculatum squamous cell carcinoma of the fingers and virus. *J Eur Acad Dermatol Venerol*. 2008;22:627–8.
9. Delahaye JF, Janser JC, Rodier JF, Auge B. Cuniculatum carcinoma. 6 cases and review of the literature. *J Chir (Paris)*. 1994;131:73–8.
10. Flieger S, Owinski T. Epithelioma cuniculatum an unusual form of mouth and jaw neoplasm. *Czas Stomatol*. 1977;30:395–401.
11. Kahn JL, Blez P, Gasser B, Weill-Bousson M, Vetter JM, Champy M. Carcinoma cuniculatum. Apropos of 4 cases with orofacial involvement. *Rev Stomatol Chir Maxillofac*. 1991;92:27–33.
12. Szmaja Z, Szyfter W, Golusiński W, Laczowska-Przybylska J, Salwa W. A rare case of carcinoma cuniculatum within the nasal cavity and paranasal sinuses. *Otolaryngol Pol*. 1996;50:325–8.
13. Huault M, Laroche C, Levy J, Laxenaire A, Roucayrol AM, Scheffer P. Epithelioma cuniculatum. Apropos of a case in the anterior gingiva with involvement of the mandibular symphyseal bone and reconstruction using a fibular osteocutaneous flap and integrated implants. *Rev Stomatol Chir Maxillofac*. 1998;99:143–8.
14. Allon D, Kaplan I, Manor R, Calderon S. Carcinoma cuniculatum of the jaw: a rare variant of oral carcinoma. *Oral Surg Oral Med Oral Pathol Oral Radiol Endodontol*. 2002;94:601–8.
15. Gassler N, Helmke B, Schweigert HG, Hassfeld S, Otto HF, Flechtenmacher C. Carcinoma cuniculatum of the oral cavity. A contribution to the differential diagnosis of potentially malignant papillary lesions of mouth mucosa. *Pathologe*. 2002;23:313–7.
16. Raguse JD, Menneking H, Scholmann HJ, Bier J. Manifestation of carcinoma cuniculatum in the mandible. *Oral Oncol*. 2006;42:173–5.
17. Kruse AL, Graetz KW. Carcinoma cuniculatum: a rare entity in the oral cavity. *J Craniofac Surg*. 2009;20:1270–2.
18. Hutton A, McKaig S, Bardsley P, Monaghan A, Parmar S. Oral carcinoma cuniculatum in a young child. *J Clin Pediatr Dent*. 2010;35:89–94.
19. Suzuki J, Hashimoto S, Watanabe K, Takahashi K, Usubuchi H, Suzuki H. Carcinoma cuniculatum mimicking leukoplakia of the mandibular gingiva. *Auris Nasus Larynx*. 2012;39:321–5.
20. Thavaraj S, Cobb A, Kalavrezos N, Beale T, Walker DM, Jay A. Carcinoma cuniculatum arising in the tongue. *Head Neck Pathol*. 2012;6:130–4.
21. Fonseca FP, Pontes HA, Pontes FS, et al. Oral carcinoma cuniculatum: two cases illustrative of a diagnostic challenge. *Oral Surg Oral Med Oral Pathol Oral Radiol*. 2013;116:457–63.
22. Goh GH, Venkateswaran K, Leow PC, Loh KS, Thamboo TP, Petersson F. Carcinoma cuniculatum of the esophagus and tongue: report of two cases, including TP53 mutational analysis. *Head Neck Pathol*. 2014;8:261–8.
23. Celin SE, Johnson J, Curtin H, Barnes L. The association of laryngoceles with squamous cell carcinoma of the larynx. *Laryngoscope*. 1991;101:529–36.