Carcinoma Cuniculatum of the Larynx

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Abstract

Carcinoma cuniculatum (CC) is a rare, distinct clinico-pathological variant of squamous cell carcinoma. Histologically it is characterized by a branching invasive growth of bland acanthotic and keratinizing squamous epithelium forming multiple, rabbit burrow-like keratin-filled crypts and sinuses. We present here a 51-year-old smoker man with a CC of the left vocal cord. The tumor was staged IA and the patient was disease-free 10 months after surgery. To our knowledge, this is the fourth case of CC of the larynx to be reported in the English literature and the first in which, for the early diagnosis, radical surgical procedures were not performed. Drawing the attention to the clinico-pathologic features of CC, we highlight that awareness of this entity and strict cooperation between otolaryngologists, radiologists and pathologists are needed for an early diagnosis that is imperative for organ-spare surgical treatment.

Keywords: Carcinoma Cuniculatum; Verrucous Carcinoma; Well-differentiated Squamous Cell Carcinoma; upper aero-digestive tract; larynx; vocal cords; histological diagnosis.

Introduction

Carcinoma cuniculatum (CC), also referred to as epithelioma cuniculatum, is a rare variant of well-differentiated squamous cell carcinoma (SCC) [1, 2]. The term *cuniculatum* refers to the complex pattern of deep invasion by keratinizing squamous epithelium lined branched rabbit burrow-like crypts and sinuses. As the CC shows, if ever, limited low-grade cytological atypia, its histological recognition may be extremely difficult, in particular on small biopsy [2-4].

First described by Aird in 1954 [1], CC may affect any cutaneous area of the body. It occurs with elective localization in the skin of the plantar surface of the foot, followed by toes and heel [2]. Rarely CC has been described in the mucosa of the upper aero-digestive tract as well [3-16].

Even though the aetiology of this tumour is not definitely established, infection, traumatic event, chronic irritation and radiation have been variably reported as possible triggering factors and

specifically in the aero-digestive tract, human papillomavirus (HPV) infection, alcohol and tobacco consumption have been considered without, however, any definitive proof [3-16].

Clinically, CC typically presents as a slow growing, painful and non-healing exophytic mass whereas histologically it shows both exophytic and endophytic growth patterns [1-3, 9, 16]. For these clinico-pathologic features CC was earlier thought to be an alternative name of Verrucous Carcinoma (VC) [13]. Indeed, it has even been described as inverted VC [11]. However, starting from 2005, the World Health Organisation (WHO) recognizes CC as a specific nosologic entity in the oral cavity [17].

Since CC is locally invasive and metastases to regional lymph nodes have been rarely described [4, 14], local resection is the only definitive treatment, which is performed without regional lymph node dissection in most of the cases.

To the best of our knowledge, CC has been described in the larynx in only three cases [4, 8, 12]. The aim of this paper is to present a rare case of CC of the vocal cord and review the pertinent literature.

Case Report

A 51-year-old Caucasian smoker man presented to the Otolaryngology clinic of our University Hospital in September 2019, with a 10-month history of dysphonia. At admission, the patient performed a flexible laryngoscopy with narrow-band imaging (NBI) that revealed a whitish mass of the left vocal cord, extended from the anterior commissure to the posterior region of the cord. Laryngeal motility was preserved, and no cervical lymphadenopathies were clinically evident.

A computed tomography (CT) of the head and neck with contrast was performed and showed a minimal local involvement of the left vocal cord, with no extension to the close structures and no cervical lymphadenopathy (Figure 1).

The patient underwent removal of the lesion through micro-laryngoscopy. Histological analysis of the sample (Figure 2) revealed a branching endophytic network of bland keratinizing squamous epithelium forming multiple, complex, branching keratin-filled crypts/sinuses “burrowing” within the superficial lamina propria. Focally, the keratin within crypts/sinuses was associated with

inflammatory cells. Dyskeratosis and intra-epithelial neutrophils and micro-abscesses were also focally observed. The lesion extended for about 3.5 mm horizontally and showed a maximum depth of about 2.0 mm. The front of invasion was bulbous and the squamous epithelium was characterized by prominent acanthosis and keratosis. A florid inflammatory infiltrate was present in the lamina propria. These findings were considered consistent with CC. Immunostaining for HPV (clone K1H8, Dako, Glostrup, Denmark) was negative.

Based on histological evaluation and clinico-radiological results and to achieve oncologic radicality, a unilateral cordectomy of the left vocal cord was performed in November 2019. Histopathologic analysis of the sample revealed mucosa lined by squamous epithelium that focally formed a minimally branching superficial crypt/sinus filled with keratin associated with a florid inflammatory infiltrate within the lamina propria that was considered a remnant of the lesion (Figure 3). The tumor was staged IA. A strict follow-up was planned. Flexible white-light and NBI laryngoscopy performed 6 months after surgery failed to detect any lesion (Figure 4). This finding was also confirmed four months later. Further close and prolonged monitoring is warranted.

Discussion

In the larynx, CC has been previously described only in three cases [4, 8, 12]. A synopsis of the main clinical data of these cases is reported in Table 1. As two of the previously reported cases [4, 12], our patient was a smoker. Unlike the case reported here, in all these cases the tumor was identified in an advanced stage that required radical surgery (partial or total laryngectomy with or without neck lymph node dissection) [4, 8, 12]. This is not a surprise because, as in other sites, the time between the onset of the tumor and the definitive diagnosis may be long and multiple biopsies may be needed. In one of these cases, in which the tumor involved the glottic and sub-glottic regions, the definitive diagnosis was made on the surgical specimen after repeated biopsies [12].

Thus, definitive diagnosis of CC may be difficult and requires clinical and instrumental examination completed by generous deep biopsies for histological examination. The need of deep biopsies is

related to the peculiar endophytic growth pattern of CC. Indeed, CC is characterized by deep and broad proliferation of keratinizing squamous epithelium virtually devoid of obvious features of malignancy which line branched, sometimes cystic, rabbit burrow-like crypts and sinuses. The possibility to identify this pattern of growth and invasion, that was observed in the first biopsy performed in the patient reported here, make easier the differentiation of CC from other squamous proliferative lesions with which it may be confused, first of all VC. Indeed, even though CC and VC may appear clinically similar and are both characterized by well-differentiated keratinizing squamous cells and minimal atypia, the pattern of invasion in VC is different and consists of broad bulbous rete ridges with pushing margins [3, 11, 14-17]. To differentiate CC and VC is mandatory because the clinical course of the former is more aggressive locally and, even if rarely, cause of lymph node metastasis [4, 11, 14-17]. Obviously, since the crypts/sinuses of CC may be inflamed/infected (as proved by the evidence of intra-luminal admixture of keratin and inflammatory cells and intra-epithelial neutrophils and micro-abscesses) reactive squamous cytological atypia, brisk mitotic activity and pseudo-epitheliomatous hyperplasia may also be observed. As a consequence, conventional well-differentiated SCC or a hybrid carcinoma (well-differentiated SCC in CC) may be suspected as well. In these cases, only the demonstration of an unequivocal stromal infiltration, for which, again, deep biopsies may be needed, let the correct differential diagnosis [12, 16, 17]. Finally, bioptic sampling limited to the superficial exophytic component of the lesion might also suggest a papillary SCC. However, this variant of SCC may be differentiated from CC (and VC as well) because it consists of thinner and more arborizing papillae invariably lined by atypical cells [14-17].

Regardless of the location, once the diagnosis is established, the prognosis of CC is good. CC may be locally destructive but lymph node metastases are rare [4, 14]. For these reasons, surgical excision/resection is the mainstay of treatment in combination with close and prolonged monitoring [4, 10, 12, 14-17]. Lymph node dissection should be considered in the case of accompanying lymphadenopathy and when the diagnosis of CC is doubtful. Due to the rarity of CC in the upper aero-digestive tract, and in particular in the larynx, and the diagnostic challenges that this variant of

well-differentiated SCC poses on biopsy, awareness of this entity and a strict cooperation between otolaryngologists, radiologists and pathologists are needed for an early diagnosis that is imperative for organ-spare surgical treatment, as in our case.

Compliance with Ethical Standards

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Ethics statement: All the clinico-pathologic investigations detailed in the manuscript have been conducted in accordance with the Declaration of Helsinki and its later amendments or comparable ethical standards.

Patient consent to participate: Written informed consent for publication of data and images was obtained from the patient.

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Table 1

Reported cases of carcinoma cuniculatum of the larynx.

Ref.	Age/Gender	Site	Smoker	Treatment	Follow-up
4	49/M	glottis and sub-glottis with involvement of a saccular cyst	+	total laryngectomy with bilateral neck dissection	disease free 6 months after surgery
8	63/M	right hemi-larynx with sub-glottic extension	not available	total laryngectomy with bilateral neck dissection	disease free 42 months after surgery
12	72/M	glottis and supra-glottis	+	supra-cricoid laryngectomy with crico-hyoidopexy extended to the pre-laryngeal muscles	disease free 70 months after surgery
present case	51/M	left vocal cord	+	incisional biopsy and cordectomy	disease free 10 months after surgery

Figure legends

Figure 1. Computed tomography images in the axial (A) and coronal (B) planes showing a minimal local involvement of the left vocal cord with no extension to the close structures and no cervical lymphadenopathy.

Figure 2. Low-power magnifications of the lesion removed through micro-laryngoscopy are shown in A and B. The images were obtained from two different histological sections. The lesion consists of a branching endophytic growth of keratinizing squamous epithelium forming crypts/sinuses "burrowing" within the superficial lamina propria. A florid inflammatory infiltrate is present in the lamina propria. Crypts/sinuses are lined by well-differentiated squamous epithelium and filled with keratin (C), that, focally, is intermixed with inflammatory cells (D). Dyskeratosis, intra-epithelial neutrophils and micro-abscesses are illustrated in E. Staining: haematoxylin and eosin. Bars: 500 μm in A and B, 100 μm in C and 50 μm in D and E.

Figure 3. A minimally branching superficial crypt/sinus was observed in the sample obtained at cordectomy. The crypt/sinus is filled with keratin and associated with a florid inflammatory infiltrate within the lamina propria. Staining: haematoxylin and eosin. Bar: 150 μm.

Figure 4. Flexible white-light (A) and NBI (B) laryngoscopy performed 6 months after surgery.