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Gingival carcinoma cuniculatum mimicking a reactive/inflammatory process

Carcinoma cuniculado gengival mimetizando um processo inflamatório/reativo

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ABSTRACT

Carcinoma cuniculatum (CC), a rare variant of oral squamous cell carcinoma, presents well-differentiated neoplastic epithelial cells infiltrating the underlying submucosal or bone tissues, forming the so-called "rabbit burrows" filled with keratin. A 67-year-old female patient was referred complaining of a painless tumoral mass in the left mandibular body, with several months of evolution. Previous history indicated extraction of the teeth #37 and #38 and diagnosis of chronic suppurative osteomyelitis. A deep incisional biopsy revealed CC. Due to its microscopic features, suggesting an inflammatory or reactive process, strict clinicopathological correlation is necessary for the correct diagnosis of CC.

Key words: squamous cell carcinoma; oral pathology; mouth; mandible; gingiva.

RESUMO

O carcinoma cuniculado (CC), uma rara variante do carcinoma espinocelular oral, apresenta células epiteliais neoplásicas bem diferenciadas que se infiltram na submucosa ou no tecido ósseo subjacente, formando a chamada "toca de coelho", preenchida por queratina. Relatamos o caso de uma paciente de 67 anos que foi encaminhada apresentando uma massa tumoral assintomática no corpo mandibular esquerdo com vários meses de evolução. A história prévia indicou exodontia dos dentes 37 e 38 e diagnóstico de osteomielite supurativa crônica. Uma biópsia incisional profunda revelou CC. Devido às características microscópicas, as quais sugeriram um processo inflamatório ou reativo, é necessário estrita correlação clinicopatológica para o correto diagnóstico do CC.

Unitermos: *carcinoma de células escamosas; patologia bucal; boca; mandíbula; gengiva.*

RESUMEN

El carcinoma cuniculatum *(CC), una variante del carcinoma de células escamosas oral, presenta células epiteliales neoplásicas bien diferenciadas que se infiltran en la submucosa o en el tejido óseo subyacente, formando la llamada "madriguera de conejo", rellenada con queratina. Reportamos el caso de una paciente de 67 años con quejas de una masa tumoral asintomática en el cuerpo mandibular izquierdo con varios meses de evolución. La historia previa apuntó exodoncia de los dientes 37 y 38 y diagnóstico de osteomielitis supurativa crónica. Una biopsia incisional profunda reveló CC. Debido a las características microscópicas, que sugirieron un proceso inflamatorio o reactivo, es necesaria una estrecha correlación clinicopatológica para el diagnóstico correcto del CC.*

Palabras clave: *carcinoma de células escamosas; patología bucal; boca; mandíbula; encía.*

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INTRODUCTION

Carcinoma cuniculatum (CC), also known as epithelioma cuniculatum, is a rare variant of oral squamous cell carcinoma (SCC), which characteristically lacks cytological malignancy[1, 2]. CC was originally described on the sole of the foot and for a long time was believed to be restricted to the skin[2]. The tumor was firstly reported by Aird *et al*. (1954), which assessed three cases of plantar CC[1,3]. Oral CC was firstly depicted by Flieger and Owinski (1977)[1,4]. In 2017, the World Health Organization (WHO) classification of the head and neck tumors defined the oral CC as a neoplasm that invades the underlying subcutaneous, submucosal, or bone tissues, forming the so-called "rabbit burrows", with keratin-filled crypts that are of utmost importance for distinguishing this neoplasm from other variants of oral SCC[1, 2, 5]. To date, approximately 50 oral CC cases have been reported, often affecting the maxilla and the mandible, followed by floor of the mouth, retromolar trigone, tonsil, buccal mucosa and tongue. Interestingly, 16 cases of gingival CC have been reported so far. In addition, CC has also been portrayed in other mucosal sites, including the penis and esophagus[1, 2, 6-9].

Although CC was included in the WHO classification[2, 10], its distinction from verrucous carcinoma (VC) remains controversial, since some authors consider CC a variant of VC, whereas others have suggested that CC represents a distinct entity with potential for local aggressiveness[2, 11]. A previous study has stated that these neoplasms represent different variants of oral SCC, and their major distinguishing features are: 1. clinically, CC exhibits a sessile pink to red mildly papillary surface or corrugated appearance, though VC typically presents as a white warty lesion with more distinctive surface projections with a verrucous/frond-like hyperkeratotic surface; 2. histopathologically, the presence of a tortuous invasive component in CC contrasts with the more subtle "invasive front/pushing border" presentation of VC[12].

Therefore, the aim of this study is to describe the clinicopathological features of an additional gingival CC. We also review the literature, emphasizing its differential diagnosis.

CASE REPORT

A 67-year-old white female patient was referred complaining of a painless tumoral mass, which presented suppuration, in the left mandibular body with several months of evolution. The medical history and extraoral examination were noncontributory, and the patient denied use of tobacco or alcohol. Previous dental history revealed extraction of the teeth #37 and #38 and diagnosis of chronic suppurative osteomyelitis in the location. Intraoral examination revealed an exophytic mass located at the left mandibular gingiva, area of teeth #37 and #38, which presented a yellow purulent secretion, spontaneously and on palpation. Radiographic examination showed an osteolytic lesion with irregular and ill-defined borders (**Figure 1**). A deep incisional biopsy was performed, which microscopically showed an exuberant, well-differentiated squamous epithelial proliferation, with frequent invaginations, delimiting pseudocystic cavities, which was filled with parakeratin and peeled cells. The fibrovascular stroma showed numerous mixed inflammatory cells. In the deepest part, it was possible to see trabecular lamellar bone and foci of osseous resorption in close relationship with well-differentiated squamous epithelial proliferation (**Figure 2**). The final diagnosis of CC was established. The patient underwent surgical resection (**Figure 3**), and the specimen showed similar histopathological features. After a one-year follow-up, the patient remains well, without recurrence or alteration.

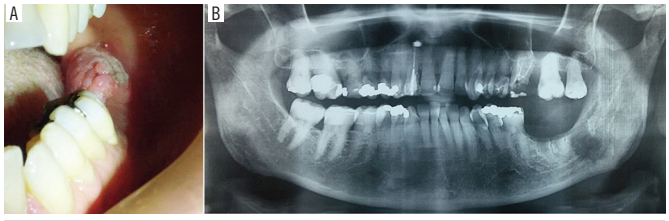

FIGURE 1 – *A) exophytic mass located at the left mandibular gingiva. Previous dental extraction and chronic suppurative osteomyelitis were noticed in this area; B) panoramic radiograph showing an osteolytic area with irregular and ill-defined borders*

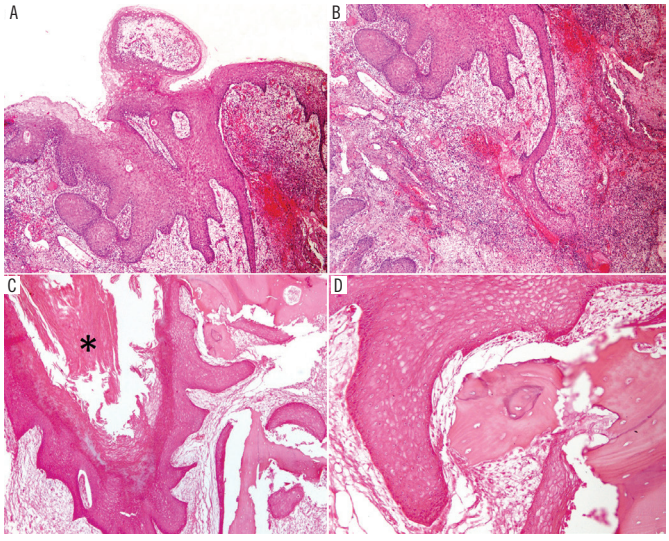

FIGURE 2 – *The microscopic analysis showed intense well-differentiated squamous epithelial proliferation, with frequent invaginations (A, 5×). The fibrovascular stroma showed numerous inflammatory cells (B, 5×). Notice the large area of keratin deposition (asterisk), foci of osseous resorption in close relationship with florid squamous epithelial proliferation with prominent invagination (C, 5× and D, 20×). Hematoxylin and eosin stain*

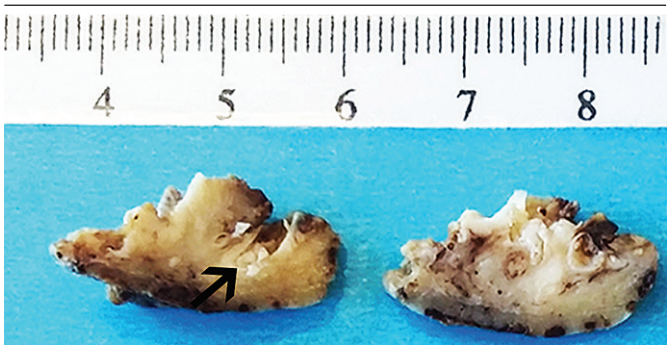

FIGURE 3 – *Macroscopic view of the surgical specimen showing several white areas, which correspond to keratin formation, reaching the basal portion of the mandible. The arrow shows the typical "rabbit burrow", which by microscopy showed similar histopathological features to those in Figure 2C (asterisk)*

DISCUSSION

CC was originally named epithelioma cuniculatum, which was believed to be restricted to the cutaneous tissue, more specifically the plantar surface of the foot. However, since its first description, it has been reported to affect non-cutaneous anatomic sites, including esophagus, larynx, penis and oral mucosa[1, 2, 7, 9, 11]. Without strict clinicopathological correlation, their diagnosis is difficult, as CC may mimic reactive or benign lesions, such as abscess, cysts, inflammatory fibrous hyperplasia and papillomatous lesion, among others[1, 2, 11].

Oral CC is a rare variant of SCC, firstly described by Flieger and Owinski in 1977[4]. Until now, approximately 50 oral CC cases have been reported[9]. In the same way as the current case, the most common site affected by CC is the mandibular gingiva[1, 2, 4, 9, 12-18], with 11 and five cases affecting the mandibular and the maxillary gingiva, respectively. In spite of this, the current case presented diagnostic difficulties such as those previously described, and only after the evolution of the tumor and consultation with the specialized service, a correct diagnosis was made. The clinicopathological features of oral CC show a wide age range (varying from 7 to 92 years) with mean age of 67 years, and slight male predilection[1, 9]. Still, in two recent case series of oral CC, a slight female predilection was observed[1, 9, 12]. Among oral SCC cases reported by Ogawa *et al*. (2004), the incidence rate of CC was 2.7%, compared with 3.5% of VC[1, 19].

It is necessary to comment that some CC cases were misdiagnosed as VC[12], thus, the true incidence of oral CC may have been underestimated. VC is also a distinct variant of well-differentiated SCC, and like CC, it is characterized by a well-differentiated epithelial proliferation with lack of overt cellular atypia. On the other hand, in VC the growth pattern is exophytic, whereas in CC the growth pattern is chiefly endophytic and infiltrative, being characterized by the presence of complex branching keratin-filled crypts. The presence of a yellowish, foul-smelling secretion (often on palpation) is a typical finding in CC and has not been described in VC[2]. Moreover, VC may eventually cause superficial bone erosion, but it does not penetrate deeply into the surrounding submucosa and bone, unlike CC[2, 7, 11, 20].

Different etiologic factors have been speculated to contribute to the development of CC, including local trauma, inflammation and radiation. Human papillomavirus (HPV) infection (HPV type 11)[21] has been shown to be present in some CC cases affecting cutaneous tissue, while other studies failed to corroborate any correlation with its oral counterpart[1, 2, 17, 20]. Risk factors such as tobacco and alcohol use have also been considered as etiologic agents; yet, most affected patients denied use of those substances[2, 15].

The histopathological analysis of oral CC, without clinical information, is challenging, especially due to lack of cytological atypia. Usually, just as occurred with the present case, a superficial biopsy at an initial stage can easily lead to misdiagnosis, such as benign epithelial lesion, pseudoepitheliomatous or inflammatory fibrous hyperplasia, and osteomyelitis[1]. In fact, after deep incisional biopsy, and strict clinicopathological correlation, we achieved the correct diagnosis.

A clinical diagnosis of oral CC should be considered when assessing a non-healing ulcer, exophytic verrucous growth, gingival enlargement of unknown origin, granulation tissue-like lesion, pebbly and fungating lesion[1]. Additionally, oral CC can also cause tooth loosening and mimic abscesses or cysts, such as illustrated in the current case and in other cases previously reported[2, 13, 15]. After review of the literature, it is evident that about one-third of the CC cases were initially misdiagnosed, delaying the appropriate management of these patients. For that reason, acquiring adequate tissue sample for microscopic evaluation in strict clinicopathological correlation is fundamental to avoid misdiagnosis[2].

Surgical excision is the treatment of choice for CC. A wide, local excision with a free surgical margin > 5 mm is recommended[22]. Even though, a recurrence of mandibular CC was reported to have a good prognosis after a second excision[16]. Despite its local aggressiveness, regional and distant metastases are very rare and the overall prognosis is good[1, 2, 14, 15]. For cases of bone invasion, a subtotal maxillectomy or mandibulectomy should be performed[1], such as described in the current case. Up to the present, there are only a few reports about chemotherapy and/or radiotherapy in the CC treatment. Because of its local aggressive behavior, the benefit of radiotherapy and/or chemotherapy is controversial. The role of radiotherapy, which some argue may provoke an anaplastic transformation, is still up for debate[1, 2].

In summary, despite several reported cases, oral CC is often misdiagnosed, especially at initial stages, and it occurred in about one-third of the cases. Oral CC often affects the mandibular gingiva, presents a slight female predilection, with

mean age of 67 years, being their clinical presentation highly variable, frequently mimicking an inflammatory or reactive process. Accordingly, strict clinicopathological correlation is essential to avoid misdiagnosis. CC should be distinguished from other oral SCC variants, notably VC. Surgical excision remains the treatment of choice for oral CC.

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