RESUMO

O tumor de células granulares (TCG) é uma lesão relativamente incomum que pode acometer qualquer parte do corpo, incluindo a orofacial. O tecido e a mucosa bucal são comuns intraorais. Apesar de casos de transformações malignas e agressivas terem sido descritos, a maioria dos TCGs são benignos. A histogênese desta lesão continua desconhecida. No entanto, estudos de imunohistoquímica e ultra-estruturais sugerem que a lesão se origina das células de schwann, músculo estriado, células mesenquimais, histiócitos e células epiteliais. O tumor geralmente ocorre em adultos idosos. A lesão é tipicamente vista como uma massa assintomática não inflamatória que mede cerca de dois centímetros de diâmetro com uma superfície de coloração avermelhada. A maioria dos tumores de células granulares são benignos cuja excisão cirúrgica é o tratamento de escolha. Em ambos os casos a ressecção com margens de segurança foi realizada sob anestesia local. As amostras foram fixadas e processadas para o estudo histopatológico. As principais características clínicas e patológicas dos casos são revisadas e discutidas.

Palavras chave: tumor de células granulares, neoplasia oral.

ABSTRACT

Granular cell tumor (GCT) is a relatively uncommon lesion occurring in almost any part of the body, including the orofacial region. The tongue and the buccal mucosa are common intraoral sites. Although aggressive and malignant variants of this neoplasm have been described, most GCTs are benign. The histogenesis of the lesion still remains unknown. However, histochemical and ultra-structural studies propose the origin of the lesion from Schwann cells, striated muscle, mesenchymal cells, histiocytes and epithelial cells. The tumor generally occurs in middle-aged or older adults. The lesion is typically seen as an uninflamed asymptomatic mass measuring about two cm in diameter with reddish surface coloring. As most granular cell tumors are benign, surgical excision of the lesion is the treatment of choice. In this study, 2 oral GCT cases are presented, corresponding to 2 male patients, with a mean age of 27 years and a mean time of evolution of the lesions of 8 months. Both lesions were located on the tongue. Differential diagnoses include fibrous hyperplasia, minor salivary gland tumor, condyloma acuminatum and neurilemmoma. In all the cases a resection with safety margins of the lesions was carried out under local anesthesia. The samples were fixed and processed for histopathological study. The main clinical pathology and diagnostic features of this neoplasm are reviewed and discussed.

Key words: granular cell tumor, oral neoplasm.

INTRODUCTION

Granular cell tumor (GCT) is an uncommon benign neoplasm, with low prevalence among soft tissue lesions that affect the oral cavity. GCTs have been reported mostly in female patients with mean ages ranging from the fourth to sixth decades of life. This tumor has received different names in addition to myoblastoma, such as myoblastic myoma, uniform granular cell myoma, embryonic rhabdomyoblastoma myoblastoma, granular cell Neutra, granular cell Schwannoma and congenital epulis. However, the name granular cell tumor (GCT) is supported by the nomenclature regulations of the World Health Assembly (WHO)1,2. Correct analysis of the histological findings plays an important role in the correct diagnosis of this...
tumor. Epithelium variations may lead to misdiagnosis of squamous cell carcinoma and consequent radical surgical excision\(^3\).

This report describes and discusses two cases of granular cell tumor involving the tongue, and reviews the literature.

**CASE 1**

A 41-year-old black male came to the Oral and Maxillofacial Surgery Outpatient Clinic of the Pernambuco School of Dentistry, University of Pernambuco (FOP/UPE) with a main complaint of a nodule on the tongue. Physical examination revealed a slightly red, raised, firm, asymptomatic lesion, 3 cm in diameter, on the dorsal surface of his tongue (Fig. 1). Results of the remaining examination of the oral cavity, pharynx and larynx were normal. He reported no previous surgical intervention in the area, and no family history of similar cases was elicited during the history taking. The patient reported that the lesion on the tongue had been present for approximately one year. No cervical adenopathy was present and there was no history of previous illness or hospitalization. An excisional biopsy was carried out and the material was sent to the oral pathologist at the Oral Pathology Laboratory of the Pernambuco School of Dentistry (LPBFOP/UPE). The histopathology showed histological sections stained with hematoxiline-eosine (HE) displaying underlying connective tissue with a large amount of granular cells in the sub-epithelial portion of the tissue far from the basal lamina (Fig. 2B-C). The photomicrographs showed pseudoepitheliomatous hyperplasia (Fig. 2A) and at higher magnification showed the typical granular and eosinophilic cytoplasm of tumoral cells (Fig. 2D). The histological diagnosis was granular cell tumor with pseudoepitheliomatous hyperplasia of the overlying squamous epithelium. The case has been under observation for two years with no clinical signs of relapse or other lesions in the oral cavity to date.
CASE 2
A 13-year-old white male was referred for evaluation of a painless swelling on the tongue with a two-year history. Clinical examination revealed a single, firm nodular mass about 4 cm in size with a reddish white cast on the dorsum of the tongue. It was mildly tender on palpation (Fig. 3). A differential diagnosis of a pyogenic granuloma, lipoma, traumatic fibroma or neurilemmoma was given. No other associated lesions were found.

An excisional biopsy was performed, which revealed histopathological features consistent with a granular cell tumor, similar to the first case. The patient is currently being monitored at six-month intervals and no signs of recurrence or any malignant transformation have been found during a three-year follow-up.

DISCUSSION
A GCT is a slow-growing tumor of undefined origin, first called “granular cell myoblastoma” based on Abrikossoff’s first report of a GCT in 1926, suggesting an apparent association between granular cells and skeletal muscle4,5. Others investigators have also suggested an origin from macrophages, histiocytes, fibroblasts and undifferentiated mesenchymal cells. However, these theories have been incompletely supported6,7. More recently, the unique granular cells that make up the tumor are believed to be of neural origin (Schwann-cell) based predominantly on immunohistochemical stains (S-100 protein and neuron-specific enolase) and scanning electron microscope studies (myelin sheath-like structure)8,9. Non-neural granular cell tumors have been described in the literature and differ from traditional GCTs in that they show expansible growth, cellular growth, cellular atypia and negative staining for S-10010. Histological findings of our cases did not present mitoses or cytologic atypia.

GCTs appear in a range of patients, from children to the elderly, but usually involve individuals in their fifth to sixth decades of life (Table 1)11,12. This report shows one patient in his fifth decade of life and another aged 13 years, who confirm the broad age-range of this kind of tumor. Most studies demonstrate a female predilection. However, apparent gender predilection may depend on tumor site. The difference varies from 2:1 female predilection for oral cavity lesions to 5:1 for larynx tumors13,14. The two cases presented in this study differ from the findings described in the literature because the patients are men and the lesions are located on the tongue.

Typically, these soft tissue lesions occur as small (less than 2 cm. diameter), well-circumscribed, solitary, painless, uninflamed, non-ulcerated nodules, as in our described cases. Tumors can occur on skin and subcutaneous tissue, and occasionally some may be identified in lung, gastrointestinal tract and heart tissue. In the head and neck, the tongue is by far the most common location for GCTs15-17, in agreement with our cases. Congenital granular cell tumor (congenital epulis) usually arises from alveolar mucosa and may occur in the mandible or tongue18.

Most GCTs are solitary; however, multiple lesions occur in 7% to 25% of the cases. Multiple tumors are most often located in the oral mucosa, skin, gastrointestinal tract, respiratory tract and biliary system19-20. GCTs are usually benign, while malignant tumors are extremely rare, making up approximately 1% to 2% of such tumors. Most malignant lesions are larger than the benign form, usually measuring more than 4 cm maximum diameter. Malignant GCTs can occur at the same sites as the benign forms and exhibit a high rate of recurrence and metastasis after surgical excision21,22. Our cases have been followed for up to three years without malignant recurrence. Pseudoepitheliomatous hyperplasia of the overlying oral epithelium is seen in a variety of cases. This

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Age (Yrs)</th>
<th>Gender</th>
<th>Race</th>
<th>Intra-Oral Site</th>
<th>Total No. of Tumors</th>
<th>Treatment</th>
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<tbody>
<tr>
<td>Apisarnthanarax</td>
<td>1981</td>
<td>39 (Mean)</td>
<td></td>
<td>62% females/38% males</td>
<td>Tongue</td>
<td>88 – 06 Oral tumors</td>
<td>Surgical Excision</td>
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<td>1988</td>
<td>-</td>
<td>2:1 Female/Male</td>
<td>-</td>
<td>Tongue (67%) Oral mucosa (13%) Lip (8%) Soft palate (6%) Other sites (6%)</td>
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<td>Okada et al.</td>
<td>1990</td>
<td>29</td>
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<td>Seki</td>
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<td>74</td>
<td>Female</td>
<td>-</td>
<td>Oral mucosa</td>
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<tr>
<td>Sica</td>
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<td>58</td>
<td>Female</td>
<td>-</td>
<td>Palate</td>
<td>02</td>
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<tr>
<td>Zahid</td>
<td>1996</td>
<td>45</td>
<td>Male</td>
<td>-</td>
<td>Oral mucosa</td>
<td>01</td>
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<td>32</td>
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<td>-</td>
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<td>Soft Palate</td>
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<td>-</td>
<td>-</td>
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<td>Van der Meij</td>
<td>2001</td>
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<tr>
<td>Xue et al.</td>
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<td>13 – Tongue 01 – Oral mucosa</td>
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<td>48</td>
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<td>Sposto et al.</td>
<td>2006</td>
<td>30-42</td>
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<td>-</td>
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<td>Surgical Excision</td>
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<td>Nagaraj et al.</td>
<td>2006</td>
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<td>Female</td>
<td>-</td>
<td>Tongue</td>
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<td>Surgical Excision</td>
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<td>Eguía et al.</td>
<td>2006</td>
<td>25-60</td>
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<td>-</td>
<td>6 – Tongue 1 – Gingiva 1 – Oral mucosa</td>
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<td>Surgical Excision</td>
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<tr>
<td>Angiero et al.</td>
<td>2006</td>
<td>28-66</td>
<td>6 Females/5 Males</td>
<td>-</td>
<td>10 – Tongue 1 – Oral mucosa</td>
<td>11</td>
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<td>2007</td>
<td>45</td>
<td>Female</td>
<td>W</td>
<td>Tongue</td>
<td>1</td>
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</table>

may be such a prominent feature that subjacent GCTs are overlooked and a superficial biopsy from a such a lesion may be misdiagnosed as a well-differentiated squamous cell carcinoma. However, pseudoepitheliomatous hyperplasia was observed in both our cases, and excisional biopsy with safety margins was carried out deeply in the lesion, where granular cells could be visualized. Oral pathologists should be careful in the analysis of incisional biopsy of tumors located on the lateral border of the tongue, since this site is one of the most prevalent locations of oral cancer. Apart from the histopathological picture, the clinical size of the tumor, pain, speed of growth, invasion of underlying and adjacent struc-
tures and the presence of regional and distant metastasis will aid in differentiating a benign GCT from a malignant lesion. The interface between surgeon and pathologist should evaluate the need for other procedures, removing deeply-located tissue, where characteristic features of the tumor are located.

In terms of differential diagnosis, other benign connective and neural tumors, such as fibromas, lipomas, neuromas, neurofibromas or schwannomas with their malignant variants should be considered. Granular cell change is a nonspecific finding noted in many tumors of the oral cavity. GCTs, congenital epulsi and odontogenic tumors such as ameloblastomas and granular cell odontogenic fibromas are among the most common tumors of the oral cavity to contain granular cells \(26-31\). Spontaneous regression has been noted but is apparently a rare event \(14\). Surgical excision is the treatment of choice for GCT regardless of whether the lesions occur as isolated tumors or demonstrate multifocal involvement \(32\). In most cases this procedure is curative, even if the tumor is incompletely excised; however, a small percentage has recurred when tumor remained in the margins of excision \(33\). Nevertheless, locally aggressive and manifestly malignant variants of this tumor have been described in the literature \(34\). In our cases no recurrences after excision have been observed to date.

The prognosis following treatment is excellent. Malignant variants, however, present 60% mortality after diagnosis, principally caused by metastasis \(1,12,15\). In this report, neither case presented malignant features.

In conclusion, GCT is a relevant pathologic entity among oral tumors, principally for great number of differential diagnosis between soft tissue lesions and for misdiagnosis of squamous cell carcinoma after an incorrect incisional or excisional biopsy and mistaken histological analysis resulting in an unnecessary radical treatment.

**REFERENCES**