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The neural histogenetic origin of the oral granular cell tumor: An immunohistochemical evidence

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Abstract

Aims: Granular cell tumor (GCT) is a rare neoplasm that can appear in any site of the body, but most are located intraorally. Its histogenetic origin remains unclear. This report analyzes the immunoprofile of 15 cases of granular cell tumors, occurring in 13 women and 2 men and the lesions were located on the tongue or upper lip. Patient age ranged from 7 to 52.

Methods: The patients demographic data and the cytological and architectural features of the lesions were analyzed in oral GCTs (n = 15). The lesions were also submitted to a panel of immunohistochemical stains with antibodies against S-100, p75, NSE, CD-68, Ki-67, Synaptofisin, HHF-35, SMA, EMA, Chromogranin, Progesterone, Androgen and Estrogen.

Results: Among the fifteen cases analyzed, the most common location was the tongue (84.6%). Histologically, the tumors exhibited cellular proliferation composed mainly by polygonal cells presenting an abundant granular eosinophilic cytoplasm. The nuclei were central, and the cell membranes were moderately clear. No mitotic figures were observed. The immunohistochemical analysis showed positivity in all cases for S-100, p75, NSE and CD-68, and no immunoreactivity for Ki-67, Synaptofisin, HHF-35, SMA, EMA, Chromogranin, Progesterone, Androgen and Estrogen.

Conclusion: The immunoprofile of granular cell tumors showed nerve sheath differentiation – lending support to their neural origin – and helping to establish a differential diagnosis between this lesion and other oral granular cell tumors, whether benign or malignant.

Key words: *Granular cell tumor, immunohistochemistry, oral neoplasm.*

Introduction

Granular cell tumor (GCT) (granular cell myoblastoma or Abrikossoff's tumor) is a tumor of uncertain origin that has been variably considered a true neoplasm, a degenerative metabolic process or a trauma-induced proliferation. Today, following the introduction of immunohistochemistry, the hypothesis of neural origin has been more widely accepted. However, reports suggesting a possible muscular, histiocytic, fibroblastic or pericytic origin can be found in the literature (1).

Although GCT may appear in any site of the body, most cases (more than 50%) occur in the mouth, more precisely on the tongue. Typically it appears as a single, sessile and asymptomatic nodule, with a smooth or pseudo-ulcerated surface, rarely greater than 3 cm. A wide age range can be affected; there is a prevalence peak between the fourth and sixth decades of life, and a predilection for females. (2).

Usually it behaves as a benign lesion; however, about 2% of the cases can present a malignant course (3). The treatment of choice is surgical excision and the prognosis is favorable due to its slow growth rate, low aggressiveness and low recurrence rates (2,3).

Although rare, GCT must be included in the differential diagnosis of other granular cell tumors of the mouth, whether benign or malignant, such as granular cell leiomyoma, non-neural granular cell tumor, congenital epulis and alveolar soft part sarcoma (4).

The present study describes the immunohistochemical profile of oral GCT, comparing it to data from the literature on other granular lesions, with the intent of providing greater knowledge to correctly diagnose and treat the ailment, and also to discuss its most likely origin.

Material and Methods

Fifteen cases diagnosed as oral GCT were selected from the archives of the Oral Pathology Service, School of Dentistry, at the University of São Paulo. Thirteen patients were women and 2 were men, and the lesions were located on the tongue (84.6%) and the upper lip (15.4%). Patients ages ranged from 7 to 52.

Histologically, the tumors exhibited cellular proliferation composed mainly by polygonal cells presenting an abundant granular eosinophilic cytoplasm. The nucleus were central, and the cell membranes were moderately clear. No mitotic figures were observed. The connective tissue was scant and fibrous (Fig. 1A). Only one case presented pseudoepitheliomatous hyperplasia (PEH) of the lining epithelium.

Diagnosis was confirmed in hematoxylin-eosin sections. Three μm thick sections were obtained from the formalin-fixed, paraffin-embedded material, and were submitted to immunohistochemical processing by the streptavidin-biotin method; the sections were developed with diaminobenzidine. The antibodies and protocols used are described in (Table 1).

Table 1. Immunohistochemical Reagents Used in GCT and protocols.

Antibody	Manufacturer	Clone	Dilution	Antigenic treatment	Incubation time
Ki-67	Dako*	MIB-1	1:75	EDTA 30'	60min.
SMA	Dako	1A4	1:200	Citric acid 30'	60min.
HHF-35	Dako	HHF-35	1:100	Citric acid 30'	60min.
S-100	Dako	-----	1:800	No treatment	-----
Chromogranin	Dako	M0-869	1:50	Citric acid 30'	60min.
Enolase (NSE)	Dako	H14	1:75	Citric acid 30'	60min.
Synaptofisin	Dako	SY38	1:200	Citric acid 30'	60min.
CD-68	Dako	KP1	1:400	Citric acid 30'	60min.
Androgen R.	Dako	AR441	1:50	Citric acid 30'	60min.
PgR	Dako	PgR636	1:25	Citric acid 30'	60min.
ER-beta	Novocastra**	6F11	1:50	Tris-EDTA 30'	60min.
EMA	Dako	E29	1:75	Citric acid 30'	60min.
P-75	Neomarkers***	NFGR5	1:200	Citric acid 30'	60min.

* Dako, Glostrup, Denmark. ** Novocastra, UK. ***Neomarkers Fremont, CA

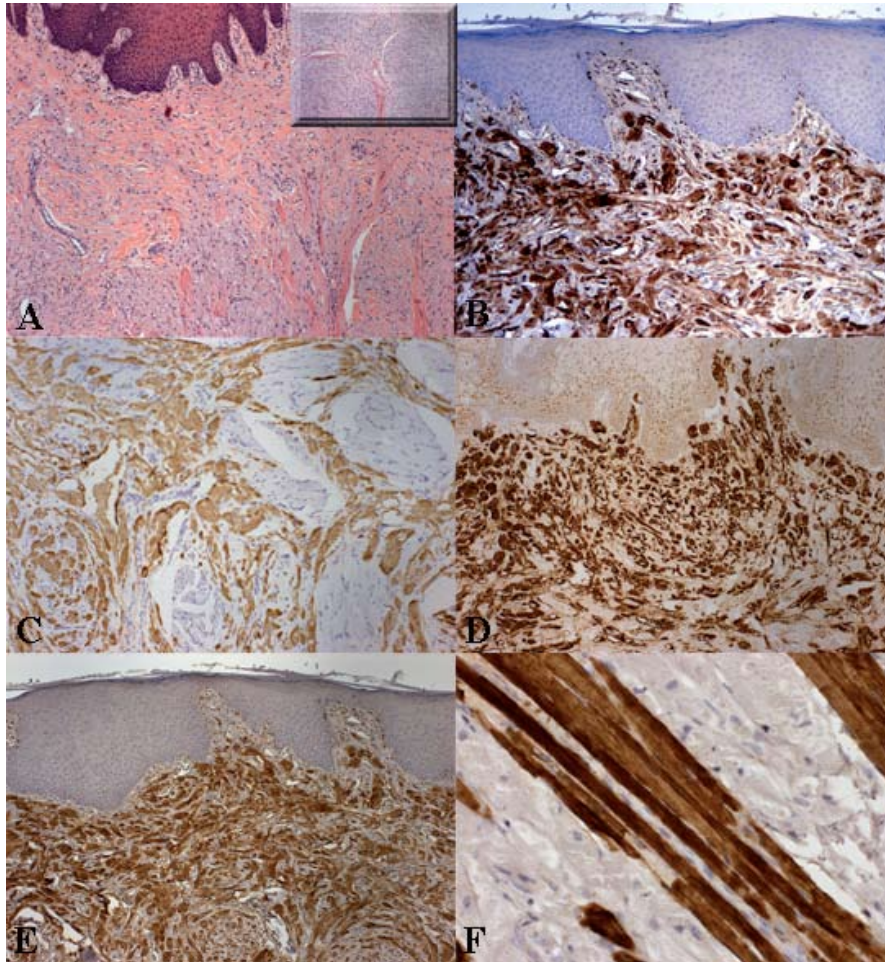


Fig. 1. (A) Histological aspect of the granular cell tumor showing proximity between the epithelium tissue and the GCT (hematoxylin and eosin, original magnification, x100). In detail – Neural arrangement of the granular cells with fibrous septum (hematoxylin and eosin, original magnification, x100). – Overexpression of S-100. Note the positivity in Langerhans cells at the basal layer (B). Positive immunoreactivity for p75 (C), CD-68 (D) and NSE (E) (Strep. Original Magnification x100). Aspect of negative expression for HHF-35, showing the positive control in muscle cells (F) (Strep. Original Magnification x400).

Results

The immunohistochemical analysis showed positivity in all cases for S-100, P75, CD-68 and NSE (Fig. 1 B, C, D, and E). On the other hand, all cases were negative to Ki-67, Synaptofisin, HHF-35 (Fig. 1 F), SMA, EMA, Chromogranin, Progesterone, Androgen and Estrogen. A comparative immunohistochemical profile between the GCT studied here and other granular lesions described in the literature is discussed below.

Discussion

In the present study, the cases of GCT analyzed were more prevalent in the tongue (84.6%), with almost all cases occurring in female patients, which is in accordance with the literature (2). Although unclear, some authors suggest that this prevalence in females could be

due to a hormonal influence in GCT etiopathogeny (5). However, in the present study the hormonal participation could not be confirmed since all immunohistochemical reactions to androgen, progesterone or ER-beta receptors were negative.

In the literature, the presence of PEH is reported as occurring in over 50% of the cases, whereas only one case presented this aspect in this study. The association the presence of PEH in GCT to some clinical parameters such as progression time and tumor location was considered. However, this association has not been confirmed by others.

Much has been discussed about the granular nature of GCT cells. Generally, it is believed that it is a response of the tissue to many factors, such as: neoplasia, degenerative or reactive processes like anoxia, metabolic

disorders and lysosomal effects (6,7). In the oral cavity, other benign tumors can present granular cells such as granular cell leiomyoma, nonneural granular cell tumor, congenital epulis and also malignancies such as alveolar soft part sarcoma (4). These entities must be distinguished from GCT, especially because of their different biological behavior.

Granular cell leiomyoma is an uncommon neoplasm in the mouth, possibly owing to the scarcity of smooth muscle in this area. When it does occur, it is usually located in the lips (primary occurrence) or the tongue, cheek, palate and gingiva (secondary occurrence). It can be observed in any age, with a slight prevalence in men (8). Immunohistochemical reactions confirm the smooth muscle origin of the cells since they are positive to smooth muscle actin (SMA) and desmin, and are negative to S-100, which is known as an important marker related to peripheral nerve sheath tumors (9).

Another important differential diagnosis is the nonneural granular cell tumor, described by Le Boit et al. (10). It differs clinically from GCT due to its expansive growth and cellular atypia. Immunohistochemically, Lerman et al. (2007) described diffuse and strong staining for CD-63 and vimentin, focal positive staining for CD-68 and smooth muscle actin (SMA), and negative staining for S-100 (11).

Congenital epulis should also be considered in differential diagnosis with GCT. These are rare tumors that can be located at the alveolar crest or in the tongue of newborn babies, with higher prevalence in females. Histologically, they are similar to GCT, and are not reactive to S-100, smooth muscle actin, CD-68 and desmin (12). Their pathogenesis is unknown, but their singular immunohistochemical pattern indicates a different origin from GCT.

Among the malignant lesions, alveolar soft part sarcoma (ASPS) can be confused with GCT due to its histological similarity. Most cases of ASPS are observed in teenagers and young adults, with a higher prevalence in females, and metastasis occurs in the lung, brain and bones (13). However, histological aspects are usually enough to differentiate both lesions, but should such aspects not suffice, PAS positivity to intracytoplasmic rod-shaped crystals in the ASPS can help. In addition, immunohistochemical reactions show focal positivity to desmin and smooth muscle actin, and negative reaction to S-100 (13,14).

Many ultrastructural and immunohistochemical studies have been made intending to explain GCT origin. However, despite the various proposed theories, its histogenesis remains uncertain (5,11,15). In the present study, the immunohistochemical reactions showed strong positivity to S-100, p75 and CD-68, suggesting a peripheral nerve sheath differentiation (neural origin). Ultrastructural studies corroborate with the immuno-

histochemical profile as these studies have shown that the intracytoplasmic granules are membrane-bound vacuoles (autophagolysosomes) (16). Additionally, it is clearly known that, when there is damage to the myelin sheath, the myelin enter into a process of disintegration and is phagocytosed initially by Schwann cells, and later by macrophages. (17,18)

The p75 positive expression has been reported as an important event that can be observed in the main neural tumors and other benign soft tumors. The importance of its expression is based on the relation between p75 and the nerve growth factor (NGF). NGF is the prototype molecule of the neurotrophin family and binds to the tyrosine kinase high-affinity receptor TrkA and to the low-affinity receptor p75. NGF is thought to be responsible for growth, apoptosis, and function of the nervous system (19).

The association of histological and clinical aspects to the immunoprofile is essential to establishing the correct diagnosis of this lesion (GCT), which is important due to the different therapeutic approaches to granular cell lesions. Furthermore, the immunohistochemical analysis made in this study broadens the knowledge about the lesion etiopathogeny.

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