International Journal of Dental Hygiene

Official Journal of the International Federation of Dental Hygienists

ORIGINAL ARTICLE

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Histogenesis of Abrikossoff tumour of the oral cavity

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Dates:
Accepted 16 August 2008

To cite this article:
Int J Dent Hygiene **8**, 2010; 53–62
DOI: 10.1111/j.1601-5037.2009.00392.x
Haikal F, Piñeiro-Maceira J, Dias EP, Ramos-e-Silva M. Histogenesis of Abrikossoff tumour of the oral cavity.

Abstract: *Background:* Abrikossoff or granular cell tumour (GCT) is a relatively rare neoplasia, benign in most of the cases. It may occur in any part of the human body, but it has an oral location in 70% of the cases. Its origin has been discussed for decades, and it is not yet definitively determined. Immunohistochemical techniques suggest its origin in the Schwann cells, while more recent studies with new markers indicate an origin related to neuroendocrine cells. *Objective:* Contribute to the clarification of histogenesis of oral Abrikossoff tumour studying immunohistochemical marking of 11 oral Brazilian cases. *Materials and methods:* Samples of tissues from the oral mucosa, tongue and lips placed in paraffin blocks, from eleven patients with a histopathological diagnosis of benign GCT were studied. Four different anti-serums (S-100, vimentin, PGP9.5 and ENE) were used for immunoperoxydase technique. *Results:* A clear positivity for S-100 protein and vimentin was observed, with markers indicating origin from the Schwann cells. Less intense positivity was found in some cases, for ENE and PGP9.5, which suggests a neuroendocrine origin. *Conclusions:* The results obtained suggest an origin from Schwann cells, but also arise the possibility of neuroendocrine origin. New methods and more specific immunohistochemical markers are needed to elucidate the origin of the Abrikossoff tumour.

Key words: granular cell tumour; immunohistochemical; neuroendocrine; Schwann cells

Introduction

Abrikossoff tumour, granular cell tumour (GCT), schwannoma or granular cell myoblastoma, is an uncommon neoplasia, benign in most of the cases that affects soft tissues, skin and oral mucosa with greater frequency (1, 2). Its histogenesis is uncertain and few tumours present so many controversies about their source cells (3). Many cell types have been implicated in its histogenesis, including muscular, mesenchymal, Schwann's, neuroendocrine cells and histiocytes (4–6). It was described in 1926 by Aleksei Ivanovich Abrikosov, a Russian pathologist (1875–1955) (7, 8). He classified GCT as having a myogenic origin (9).

The first Brazilian case was reported in 1970 by Sequeira *et al.*, who considered it as a granular cell myoblastoma (10). Oliveira & Taube had doubts about the cell origin and preferred to consider it of mesenchymal origin (11).

Williams & Williams suggested a neuroendocrine origin of the tumour, based on immunohistochemical results (1). Reichler *et al.* believe in a Schwann cell origin, for the tumour cell morphology being similar to its phagocytic form (12).

An additional support for origin of the Abrikossoff tumour in the Schwann cells is the presence of vimentin, also found in schwannoma, and immunoreactivity for the lineage marker of the neural crest, S-100. Demonstration of vimentin, however, is unspecific (1).

The antigen-melanoma associated and the neuron-specific enolase (NSE) are tumour markers with origin in the neural crest present in GCT, but not in Schwann cells (1).

Although many researchers, based on immunohistochemical studies and electron microscopy, favour Schwann cells as origin of this tumour, calling them granular cell schwannomas, there are some differences between the ultra-structural characteristics of schwannomas and GCT, as well as different expressions of some immunohistochemical markers (13).

Other researchers believe that the GCT is not a specific entity, but a modification that can occur not only in the Schwann cells, but also in a variety of other normal and neoplastic cells. Until further researches are carried out, the designation of GCT continues appropriate (13).

Literature review

Many tumours of the oral cavity contain granular cells in different proportions as characteristic components of histopathology, among them the odontogenic granular cell fibroma and granular cell ameloblastoma, besides variants of dermatofibroma, fibroxanthoma, angiosarcoma and carcinoma of the basaloid cells (14–18).

One of the more common granular cell lesions of the head and neck is the GCT. This tumour usually occurs between the second and sixth decade of life in greater proportion among women and blacks. It can occur in any part of the body. The head and neck are affected respectively in 45–65% of the cases. Seventy per cent are located inside the oral cavity (tongue, buccal mucosa, hard palate) especially on the tongue (19–23). There are rare congenital cases (24).

Most of the lesions of the oral cavity present as papule or nodule of less than three centimetres in diameter. They are asymptomatic and are generally covered by mucous membranes of normal aspect; but can also be verrucous (3). Lesions are mostly solitary (25).

Eight reports of Abrikossoff tumour cases were found in the Brazilian literature, with the first one in 1970 by Sequeira *et al.* Only one of those cases was located in the oral cavity (tongue) (10). The number of reported cases is low as it is a rare tumour. Until 1969, the total documented cases were estimated in around five hundred and fifty, without any other statistics found after that date (26–29).

The diagnostic confirmation is histopathological, but can be supplemented by magnetic resonance or computer contrast tomography (8, 23).

The benign form, which is predominant, shows very characteristic granular cells, of large size, polygonal or fusiform, separated by collagen, not encapsulated, with a small nucleus, abundant cytoplasm and fine eosinophilic granulations in its interior (6, 30). These granules are believed to be phagolysossomes, suggesting a degenerative process associated to these granular cells (31). The malignant form, however, is associated to a high mitosis rate and pleomorphic cell tissue (8, 23).

In 1998, Fanburg-Smith *et al.* adopted criteria for malignity and prognosis of this tumour. Six histological criteria were established: necrosis, distribution of the cells in fusiform strings, large nucleus with vesicular core, increased mitotic activity, increased nucleus radius in relation to cytoplasm and nuclear pleomorphism. Neoplasia presenting three or more of these criteria are classified as histologically malignant, those with one or two criteria are classified as atypical; those presenting only focal nuclear pleomorphism, without any additional criterion, are classified as benign (32). In some cases, a clinical-pathological correction of the diagnosis is necessary (33).

When malignant, the tumours can occasionally present local aggressiveness and, in 2% of the cases, distant metastases (regional lymphnodes, bones, peripheral nerves, peritoneal cavity and lungs) (8, 34). Surgical excision has to be performed

with recurrence in 8% of the cases, if the borders are free of lesion, and in 21–50%, when compromised (8, 23).

In 1871, a rare and well recognized tumour with significant component of granular cells was described by Neumann in children. It was the congenital epulis of the newborn, also known as gingival congenital granular cell tumour. This term suggests that the lesion is a clinical variant of the granular cell tumour, which does not proceed, because it exhibits different ultra-structural and immunohistochemical characteristics. Congenital epulis of the newborn is the most accepted term and widely used for this tumour of uncertain histogenesis (35–37).

The first case of GCT described by Abrikosov in 1926 was located on the tongue (9, 40). At the time, he proposed a myogenic origin, deeming that the tumour was the result of cell degeneration of the striated muscles, and thus classifying it as a myoma (8, 9). Since then, discussions have arisen regarding the origin of the tumour (11). In 1931, due to the finding of analogies between myoblasts and granular cells of the tumour, Abrikosov called it myoblastoma (41).

Through immunoenzymatic studies, other authors agree with the neurogenic origin (11). Histiocytic origin of GCT was proposed by Whitten in 1968, who found immunohistochemical positivity for alpha-1-antitrypsin in some tumours (42). In 1984, an ultra-structural study carried out by Thompson revealed that GCT had direct continuity with the striated muscle. Since then, other investigators have proposed a neurogenic origin based on the association of this tumour with nerves and neurofilaments. This theory was sustained by Holland *et al.*, who demonstrated positivity for S-100 in neurons and Schwann cells, but not in muscular fibres (8).

The benign granular cell tumours are, in most reports, specifically S-100 and/or neuron enolase positive (43).

Granular cells are strongly positive for the S-100 (3) protein, but there are studies reporting granular cell tumours located in lower lip and neck whose cells are negative for that protein, with these results being different from the majority (43, 44).

In a series of nine intra-oral cases of GCT, there was positivity for PGP9.5, NSE and S-100, in contrast to negativity of those markers in twelve cases of neurilemomas of head and neck. There were similar reactions with S-100, PGP9.5 and chromogranin A in five cases of neuroendocrine tumours, strongly suggesting that granular cell tumours may have a neuroendocrine nature. Positivity for chromogranin A occurs only in neuroendocrine tumours producers of catecholamines (1).

Six cases of granular cell tumours located in back, inguinal fold, abdomen, face and neck showed positivity for PGP 9.5, NK1/C3 and protein S-100, in a study carried out by Mahalingan *et al.*, favouring a neuroectodermal origin (45).

Billeret-Lebranchu *et al.*, in a study with fifty-six cases of granular cell tumours using vimentin, NSE, protein S-100 and NK1/C3, demonstrated positivity in all cases, but S-100 and NK1/C3 were the most regular, suggesting neurogenic origin (46).

Regezi *et al.* carried out a study with twenty-six cases of GCT from eighteen different sites (nine in the oral mucosa), using cytokeratin, vimentin, actin, alpha-1-antitrypsin, HLA-DR and S-100. Vimentin and S-100 were positive in all cases, and alpha-1-antitrypsin was positive in only a single case, while cytokeratin, desmin and actin resulted negative. HLA-DR was positive in eight cases. This study indicates great antigen heterogeneity in GCT lesions (47).

A study performed by Miettinen *et al.*, with vimentin and lysozime, in a set of fifteen GCT cases, with five in the tongue, found positivity for vimentin and negativity for lysozime (histiocytic marker). These results do not confirm a specific cell type for the histogenetic origin of GCT, but suggest that they may derive from mesenchymal nerve-related cells (48).

A study by Le *et al.* showed positivity in twenty-nine cases of GCT (with nine in the oral cavity) by PGP9.5, S-100, CD68 and inhibitin-alpha. The expression of inhibitin-alpha in GCT is not yet clarified; PGP9.5 and S-100 strengthen the neural origin (49).

Fine and Li demonstrated positivity for S-100, inhibitin-alpha and calretinin in a series of GCT cases. Calretinin is a calcium-binding protein, primarily a neuronal protein, favouring differentiation and neural origin (50).

CD68 is a glycoprotein expressed by myeloid precursors, cells of the mononuclear phagocyte system (macrophages) and other cells rich in lysosomes. Its positivity in GCT is attributed to an intracytoplasmatic accrual of phagolysosomes and does not reflect the histiocytic origin of the tumour (49). NK1/C3 is the neuroectodermal and lysossomal marker, reacting with cells in tumours originated from the neural crest, as melanoma (43). Inhibitin-alpha is a subunit of the inhibited glycoprotein, normally secreted by granular ovarian and testicular Sertoli cells. The expression of inhibitin-alpha is associated to sexual lineage cells and to the differentiation of steroidal cells in normal and tumour tissues (49). Murakata & Ishak reported, in 2001, the expression of inhibitin-alpha in GCT of the gallbladder and extra hepatical ducts (51). In a study carried out by Le *et al.* and another by Fine & Li, a similar expression of inhibitin-alpha in GCT of the head and neck and other sites were found; however, they concluded that such reactivity did not reflect sexual or steroidal lineage. The relationship between inhibitin-alpha and the pathogenesis of GCT is not clear (49). Calretinin is a neuronal non-specific marker (50).

After analysis of the above-mentioned studies, it became evident that the antibodies below are those of greater relevance in the evaluation of the histogenesis of GCT, being listed in Table 1 and used in the present work.

PGP9.5 (human gene protein)

Monoclonal antibody – an ubiquitin carboxyl-terminal hydrolase. It is a neuron-specific protein, being one of the most abundant brain proteins, structurally and immunologically distinct from a neuron-specific enolase. It is a marker for nervous and neuroendocrine tissues, found in neurons and in all types of human neuroendocrine cells. Its function is unknown, being considered as a new marker of granular cell tumours (47, 52). PGP9.5 and NSE are neuroendocrine markers of proven usefulness in neuroendocrine detection and differentiation; recently PGP9.5 has been showing more specificity (1).

S-100

Polyclonal antibody – the term 'protein S-100' was originally employed in the description of an acid protein fraction of the bovine brain, so designated for its solubility in saturated ammonium sulphate (53).

It is present in glial cells, Schwann cells, condrocytes, melanocytes, Langerhans cells and in related tumours (53, 54).

Immunohistochemical studies carried out using the S-100 protein demonstrated its location in the glial and neuronal cells. In the peripheral nervous system they were found in the Schwann cells (55).

Neuron-specific enolase

Monoclonal antibody; NSE glycolytic enzyme was described first in 1965 (1). It was believed to be found exclusively in the central neurons, but was later found in peripheral nerves and in some neuroendocrine cells (56).

Table 1. **Immunohistochemical differences between Schwann cell and neuroendocrine cell**

Antibody	Schwann cell	Neuroendocrine cell
PGP 9.5	+/−	+
S-100 protein	+	+/−
ENE	−	+
Vimentin	+	+/−

Immunohistochemical reaction (+) reacts; (−) does not react; (+/−) reacts weakly.

Used as marker to define neuroendocrine tumour histogenesis (52, 57).

The NSE is present in neural cells, neuroendocrine cells, but absent in Schwann cells. NSE is identified in granular cell tumours (1, 58).

Vimentin

Monoclonal antibody – intermediate filaments are proteins present in probably all nucleated cells as integrating structures. There are five proteins of the intermediate filaments, biochemical and immunologically distinct, expressed in different cells. One of these proteins of the intermediate filament is vimentin. Therefore, it can be used as marker for cell differentiation tumour origin (48).

In a work by Ophir *et al.* in granular cell tumours, only vimentin, among the five proteins of intermediate filaments, was positive in the cells, suggesting the use of those antibodies as histogenetic markers for these tumours (59).

Vimentin reacts with mesenchymal cells and seems to be located mainly in the immature glia, and it is widely found in schwannomas (1, 54, 60).

Objectives

- To study and analyse the histogenesis of the Abrikossoff tumour of the oral cavity, using four antibodies commonly employed in evaluation of neoplasia of the neural and/or neuroendocrine lineage, in immunohistochemical technique.
- Analyse the differences found in GCT in staining by the haematoxilin-eosin (HE) method.

Material and methods

Samples of oral cavity tissues from 11 patients (eight females and three males and ages between 14 and 52 years) with lesion of the buccal mucosa, tongue or lips and histopathological diagnosis of Abrikossoff tumour were blocked in paraffin. Seven cases were from the Pathology Sector of University Hospital Antônio Pedro; one case from a private laboratory; and three cases from the Pathology Sector of University Hospital Clementino Fraga Filho.

This study was approved by the University Hospital's Ethics Committee, prior to its beginning, which also authorized the researchers to use the Abrikossoff tumour's biopsy materials stored in the Pathology Sectors of the laboratories involved, due to the impossibility to obtain written authorization from the patients.

Histological sections of five micrometre thickness were obtained and processed, according to the immunoperoxidase technique in incubation with four antibodies: anti-PGP9.5, anti-S-100, anti-NSE and anti-vimentin, in following dilutions: 1:20, 1:100, 1:100 and 1:100 respectively, all from the Novocastra Laboratory.

We also analysed histological sections stained by the HE method.

Results were referred as with positivity when:

- Located focally – some limited areas.
- Located diffusely – dispersed areas.
- Light intensity – little stained (light brown).
- Moderate intensity – little more evident colouration (brown/brownish).
- Marked intensity – stronger colouration (brown).

Controls

Normal nervous tissue observed on the sides of the tumour was used as positive internal control for S-100; for PGP9.5 and NSE, endocrinal cells of the normal pulmonary tissue, and for vimentin, sample of schwannoma. As negative control, the primary antibody was not included in the technique.

Results

Eleven samples of eleven different patients with anatomical location in the oral cavity were studied, including tongue Figs 1 and 2, lips (Fig. 3) and buccal mucosa. The histopathological findings, in all cases, showed nests and/or more diffuse areas of large, polygonal cells, with small nucleus and abundant granular eosinophilic cytoplasm.

Pseudoepitheliomatous hyperplasia was also evidenced in almost all cases (Figs 4 and 5), except in case 1. In cases 3, 4 and 9, it was exuberant and irregular; in case 2 it was mild; in cases 5, 6, 7, 8, 10, and 11, it was moderate. There was a great variation in tumour morphology.

In relation to the disposition, the tumour cells of cases 1, 2, 7, 8, 9 and 10 were compacted, distributed along the whole extension of the dermis, and with imprecise limits; in cases 3, 4, 5 and 6, albeit also compacted, and the tumour cells presented delimited areas with surrounding muscular tissue (Fig. 6).

The immunohistochemical findings are summarized in Table 2. Most of the cases showed marked positivity (3+) for S-100 protein and vimentin diffusely in the nucleus and cytoplasm of the tumour cells; in two cases, the reaction was moderate (2+). One case was negative (0) for neuron-specific enolase, six cases showed slight positivity (1+) and four cases showed moderate reactivity (2+). In relation to PGP9.5, two cases presented moderate reaction (2+) in the granular cells, while four were negative (0), and five exhibited slight positivity (1+) (Figs 7–11).

Table 2. **Immunohistochemical findings in 11 cases of GCT of the oral cavity**

Case	Gender	Location	S-100	Vimentin	ENE	PGP9.5
1	W	Tongue dorsum	3+/D	3+/D	2+/D	0
2	W	Lip	3+/D	3+/D	0	1+/F
3	W	Tongue side	3+/D	3+/D	2+/D	0
4	M	Tongue	3+/D	3+/D	1+/F	1+/D
5	W	Tongue tip	3+/D	3+/D	2+/F	1+/F
6	W	Tongue	3+/D	2+/D	1+/F	0
7	W	Tongue dorsum	3+/D	3+/D	1+/F	1+/D
8	M	Buccal mucosa	3+/D	3+/D	2+/D	1+/D
9	M	Tongue tip	2+/D	3+/D	1+/F	2+/F
10	W	Tongue	3+/D	3+/D	1+/D	2+/F
11	W	Lip	3+/D	3+/D	1+/F	0

Positivity intensity graduated in a scale of negative 0, mild; 1+, moderate; 2+, marked; 3+, D-diffuse; F, focal; M, man; W, woman; GCT, granular cell tumour.

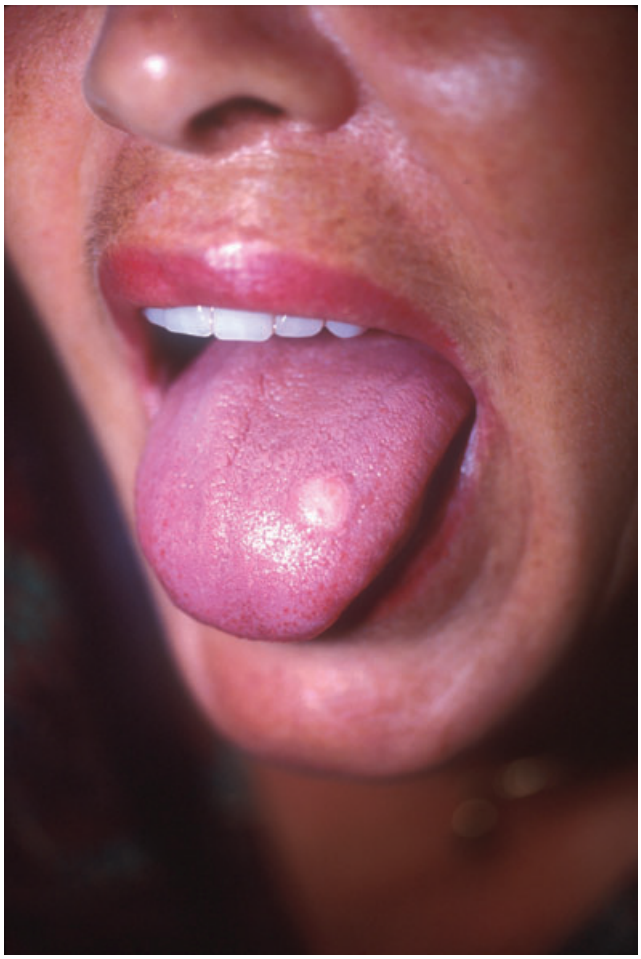

Fig. 1. Case 3 Abrikossoff tumour of the dorsum of the tongue.

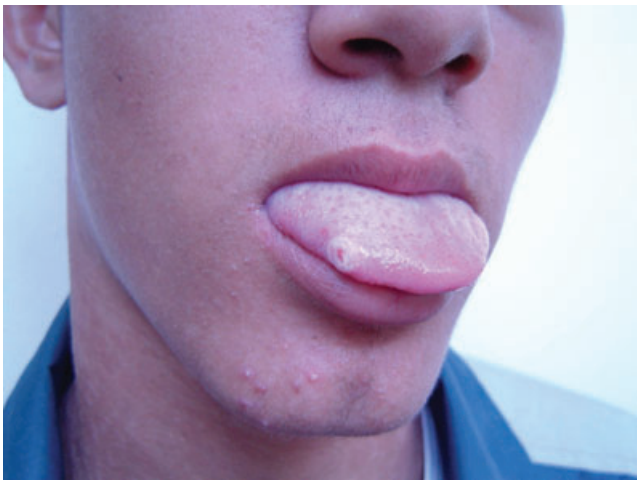

Fig. 2. Case 9 Abrikossoff tumour of the right side of tongue.

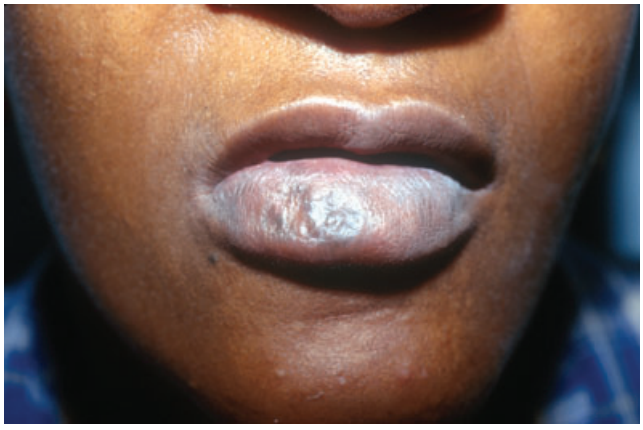

Fig. 3. Case 11 Abrikossoff tumour of the lower lip.

In case 2, nervous strands stained with S-100 were observed. PGP9.5 was positive also in the walls of blood vessels and in some nervous strands. In case 5, slight positivity in nerves and walls of blood vessels was observed.

Discussion

In this study, there was a prevalence of cases of granular cell tumours in females, with the patients' ages varying from 14 to 52 years (average 40 years). Most of the cases were located in the tongue, where there is a greater occurrence of GCT. All these data are in accordance with the literature (23). In the studied casuistic, data as gender, age and location of the lesions did not influence results.

The histopathological analysis showed that GCT may be well present as well delimited, affecting the dermis focally, or poorly delimited, being distributed and more diffused. Ten cases presented pseudoepitheliomatous hyperplasia and, in one case, this

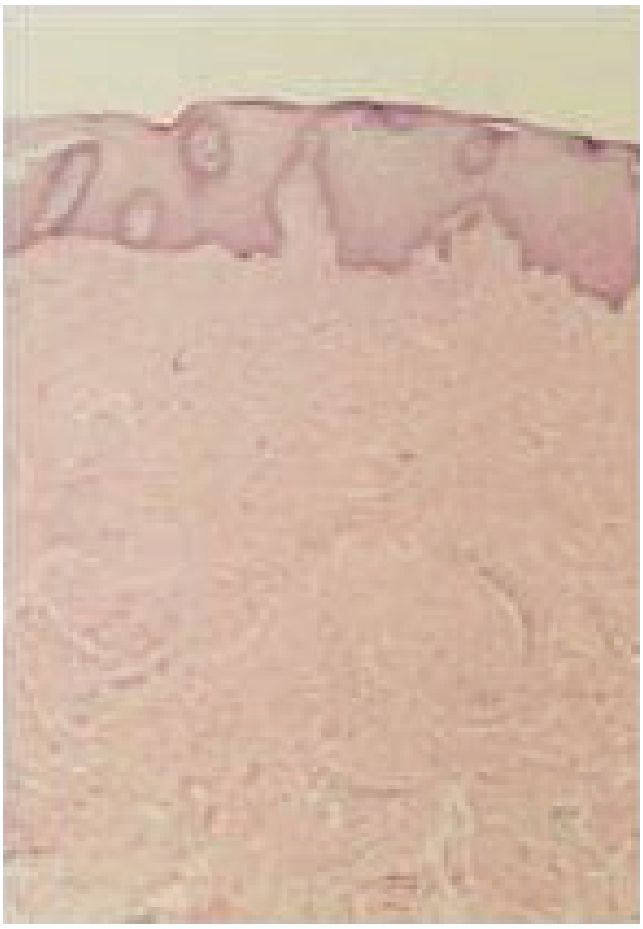

Fig. 4. Case 2 epidermal pseudoepitheliomatous hyperplasia – granular cells scattered in all dermis.

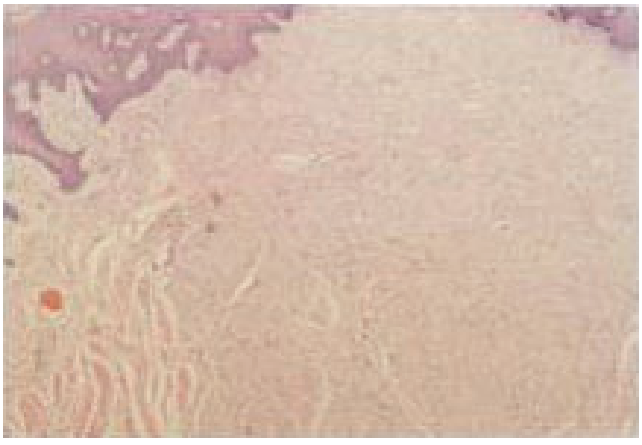

Fig. 5. Case 3 exuberant pseudoepitheliomatous hyperplasia compacted tumoural cells limited to muscular tissue.

was not demonstrated. The highly irregular or milder pseudoepitheliomatous hyperplasia is a characteristic, but not invariable aspect of the granular cell tumours, and can be taken mistaken as squamous-cell carcinoma in a superficial biopsy (61).

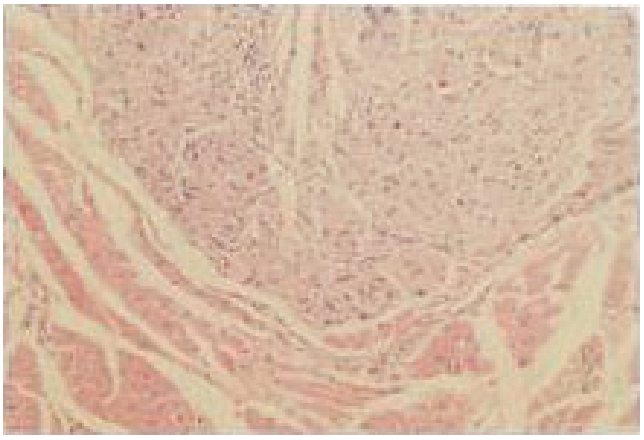

Fig. 6. Case 3 detail of the intimal relationship between granular cells and muscular tissue.

Fig. 7. Case 7 PGP9.5 mild positivity of granular cells.

Fig. 8. Case 4 S100 marked positivity of granular cells.

Although GCT is a well recognized entity, its biological nature and histogenesis remain controversial. No immunohistochemical study aiming its histogenetical clarification was found in the Brazilian casuistry.

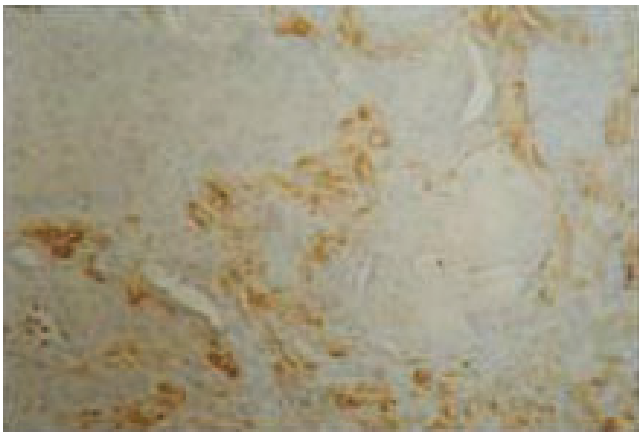

Fig. 9. Case 9 S100 positivity in cells granular detail of the pseudoepitheliomatous hyperplasia.

Fig. 10. Case 1 ENE moderate positivity in granular cells.

Fig. 11. Case 4 vimentin marked positivity in granular cells.

Some immunohistochemical studies suggest their origin in the Schwann cells, while more recent ones, using new markers, indicate an origin in the neuroendocrine cells. In this work, the neuroendocrine and/or from Schwann cells origin in granular cell tumours was questioned.

S-100 protein has been demonstrated in neurons and glial cells. In the peripheral nervous system, it is found in the Schwann cells. According to the data in the literature, it is the most frequently used marker in the definition of the GCT histogenesis, corroborating the neural origin, more specifically in Schwann cells, due to positive reactivity also in schwannomas (55).

The reactivity for S-100 is also used to confirm the GCT diagnosis, mainly when there are small samples of biopsied material, and marked pseudoepitheliomatous hyperplasia mimetizing Squamous-cell carcinoma (CEC), or in the distinction of other neoplasia with abundant granular eosinophilic cytoplasm (49). This study confirms the well established diffuse immunoreactivity of GCT with S-100 protein. The expression of S-100 sustains the hypothesis that the Abrikossoff tumour has origin in the Schwann cells.

Vimentin suggests mesenchymal origin, however it is also expressed in other cells, as histiocyes, condrocytes and endothelial cells, being thus unspecific. The intense positivity seen in the casuistry of schwannomas supplements the hypothesis of origin in the Schwann cells (1, 60). Our casuistry showed a diffuse pattern of positivity for vimentin in all cases, which together with the positivity of S-100 strengthened the origin in the Schwann cells. Vimentin would have advantages as an additional support in the confirmation of the origin in the Schwann cells, without its use being indicated for the definition of the histogenesis of the tumour.

The NSE is a more specific marker for the definition of the histogenesis of GCT. It is found in nerves and peripheral neurons and much used as marker of neuroendocrine cells, not reacting with Schwann cells (1, 57).

PGP9.5 is considered a new marker for neuroendocrine tumours. It is found in neurons and in all types of neuroendocrine cells in adults' human tissues (58). Its positivity strengthens the origin of GCT as being neuroendocrine (1).

In our study, the moderate or weak positivity for NSE and PGP9.5, with more focal pattern, does not favour the neuroendocrine origin, but does not discard it, because as already indicated previously they are the markers presently more used to define this origin (1). NSE does not react with Schwann cells and presented a moderate diffuse pattern in three cases and one in a focal case. The results obtained with those two markers diverged in relation to the majority of the cases studied in literature that reported positivity in all GCT cases submitted to the immunohistochemical technique (3, 44–46).

Other markers are not relevant for definition of the origin of GCT. Chromogranin showed negative reaction in the study by Williams *et al.*, because its positivity only occurs in neuroendocrine tumours producers of catecholamines (not being the case of GCT) (1). CD68 is expressed in rich lysosome cells, as the granular cells being used for the diagnosis of the tumour and not in its histogenesis. Collagen type IV is a product of the epithelium, endothelium and perineural cells and does not define histogenesis. HLA-DR is found in macrophages, Langerhans cells, lymphocytes B and also in non-lymphoid cells; their expression in the granular cells does not assure their origin from them, but is more linked to its immunological function. The negativity for desmin and actin, reported by Regezi *et al.*, weakens the hypothesis of origin in muscle cells (47). Calretinin and inhibitin-alpha are still little known, with only one study carried out with calretinin, and two with inhibitin-alpha, requiring more studies with GCT (50).

Based on the presence of some lysossomal enzymes, commonly also seen in histiocytes, Azzopardi suggested a histiocytic origin (62); however, the absence of lysozime and alpha 1-antitripsin, a histiocytic marker, in GCT does not confirm this hypothesis (48).

Although almost all the GCT studied in this work seem to have origin in the Schwann cells, different patterns of immunoreactivity are found in literature, suggesting that some other cells or mechanisms can be involved. It is possible that the GCT appears from more than one cell type, justifying the great difficulty of defining their histogenesis from a single origin.

Many authors consider GCT as a true neoplasia, while others have been suggesting that it represents a degenerative alteration or an abnormal metabolic process (55).

Some authors believe that this tumour presents so many controversies because the epithelial, mesenchymal and neurogenic cells originate from a common cellular precursor (22).

It is known that Schwann and neuroendocrine cells have origin in the neural crest, what may justify the positivity of all the markers, although in different intensities and patterns.

On the other hand, these results can be associated to the low sensibility of the immunoperoxidase technique for determination of the histogenesis.

Conclusions

According to the results obtained, it can be concluded that:

- The GCT is immunoreactive in immunohistochemistry with the four tested markers: anti-PGP9.5, anti-S-100, anti-NSE and anti-vimentin.
- The origin of the Abrikossoff tumour in lesions of the oral cavity is in the Schwann cells, although a neuroendocrine origin cannot be ruled out.

- There is no specific immunohistochemical marker to define the histogenesis of GCT.

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