Granular Cell Tumor of the Tongue
—A Morphological Report of a Case with Particular Reference to Histogenesis—

by

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Introduction

Oral granular cell tumors (myoblastomas) are relatively uncommon [1]. The tumor is usually divided into three varieties; common, congenital epulis (granular cell ameloblastoma) and malignant granular cell tumors [2]. The common type is usually solitary and the most frequent site of presentation is the tongue [3–5]. The histogenesis and the nature of these tumors are still controversial [1].

Many investigators have described the origin of granular cell tumors as myoblasts [4,6–10], fibroblasts [5], histiocytes [11,12], Schwann cells [13–16], epithelial cells [17] and undifferentiated mesenchymal cells [18,19]. Most authors now believe that the tumor is not derived from a single cell type [21–25].

Recently we had a case of a granular cell tumor of the tongue. In this study we examined our present case using light and electron microscopy in addition to the immunohistochemical method for myoglobin, and discussed the histogenesis and the nature of granular cell tumors.

Case Report

A 38-year-old nurse noticed a painless, yellowish-white, relatively hard and poorly circumscribed nodule on the right border of her tongue 3 months prior to her first dental examination (Fig. 1). The nodule measured about 0.8 cm in diameter and it seemed that the nodule had increased in size. Other clinical abnormalities were not found.

Methods

Light Microscopic Examination: The tissue was fixed in 10% buffered formalin and embedded in paraffin. The sections were stained with H.E., PAS (with and without diastase digestion) and azan Mallory.

Immunohistochemical Examination for Myoglobin: An immunohistochemical technique using the peroxidase-antiperoxidase (PAP) method of Sternberger et al. [26] was applied in the following order: 1) sections were deparaffinned in xylene...
and placed in absolute ethanol: 2) endogenous peroxidase activity was blocked with a 30 min. incubation in 0.3% H₂O₂ in methanol: 3) after hydration in graded alcohols and phosphate-buffered saline pH 7.4 (PBS) containing normal goat serum 1/20 for 10 min., the sections were incubated with rabbit anti-human myoglobin (Milis-Yeda Ltd., Israel) 1/40 for 30 min.: 4) following a wash in PBS, goat anti-rabbit IgG (Milis-Yeda Ltd., Israel) 1/20 was applied for 30 min.: 5) after another wash in PBS, the sections were incubated with PAP reagent (Dakopatts A/S, Denmark) 1/20 for 30 min., then washed in PBS: 6) the site of peroxidase localization was visualized by developing in freshly made 0.003% 3,3'-diaminobenzidine in 0.05 M Tris buffer pH 7.6 with hydrogen peroxide for 5–10 min.: 7) after counterstaining with hematoxilin, the sections were dehydrated in graded alcohols, cleaned in xylene and mounted. The specificity of the immunostaining was verified by replacing the primary antibody with normal rabbit serum of comparable dilution. To increase the antigenicity the sections were incubated with 0.1% protease (type VII, Sigma Chemical Co., London) for 5–15 min. at room temperature before treatment with normal goat serum [27].

Electron Microscopic Examination: The tissue was fixed in 2.5% glutaraldehyde, washed in cacodylate buffer pH 7.4, postfixed in 1% osmium tetroxide and then embedded in Araldite. Ultrathin sections were examined with a JEM T-8 electron microscope.
**Result**

Light Microscopic Observations: The tumor revealed a cellular arrangement and growth pattern of typical granular cell tumors. Marked pseudoepitheliomatous hyperplasia of the overlying epithelium was present (Fig. 2). The tumor was composed of irregularly arranged nests and cords of large, polygonal cells having granular cytoplasm and relatively large dark nuclei. The cell cytoplasm contained small, fine acidophilic granules that were positive with periodic acid-Schiff stain (Fig. 3). The cell borders were often distinct, although syncitial aggregates were also frequently observed. Small spindle-shaped interstitial cells and lymphocytes were present in varying numbers in the stroma of the tumor. A small number of collagen fibers and blood vessels were also observed. The tumor cells infiltrated to the adjacent connective tissue and striated muscle.

Localization of Myoglobin: The striated muscles adjacent to the tumor cells were also positive, whereas the tumor cells were negative (Fig. 4).

Electron Microscopic Observations: The tumor cells containing numerous granules were mostly large round or polygonal shaped. The nuclei of the tumor cells usually had one or more distinct nucleoli and were large and invaginated in places. Chromatin was evenly distributed, but usually showed a thin peripheral condensation. There were numerous small and large unit membrane-delimited bodies (granules) in the cytoplasm of the tumor cells. The majority of these bodies were relatively small and uniform in size. Some appeared almost empty, while others contained dense osmophilic amorphous materials. Myelin figures and angulate bodies were often observed in the cytoplasm of the tumor cells. Other cytoplasmic...
Fig. 3 Medium-power view showing the tumor cells having fine positive granules with periodic acid-Schiff stain.

Fig. 4 Low-power view of the tumor in the section for localization of myoglobin. The granular cells are not positive, but the skeletal muscles adjacent to the tumor cells are positive.
Fig. 5 Note the presence of numerous granules and cell membranes completely coated by basement membrane (BM) (×5600).

Fig. 6 Note two lymphocytes in the stroma (×6000).
Fig. 7 Note undifferentiated mesenchymal cell in the stroma (×6000).

Fig. 8 Note the lymphocyte-fibroblast interaction in the stroma (×5600).
organelles such as mitochondria, r-ER, and microfilaments were seldom found. Golgi's complex was not distinct. The plasma membrane was completely coated by basement membrane and invaginated in places (Fig. 5). In the intercellular spaces containing collagen fibers a small number of lymphocytes, fibroblasts, and undifferentiated mesenchymal cells were observed (Fig. 6, 7, 8). Lymphocyte-fibroblast interactions were often present (Fig. 8).

**Discussion**

Ever since granular cell tumors were first described as a specific tumor in 1926 [4], many investigators have discussed its histogenesis and nature.

There are many theories on the histogenesis of this tumor. The precursor cell for granular cell tumors was classically thought to be a myoblast based on light microscopic observations [4,6–10]. Other theories regarding its histogenesis include a fibroblastic [5], a storage-cell [11,12] and an epithelial origin [17]. Recently some investigators have suggested the concept that granular cell tumors are of a neural origin [3,13–16,28–30], especially Schwann cells [13–16]. This concept was based on light and electron microscopic observations showing that the tumor cells were within peripheral nerve sheaths. Concentric masses of the tumor cells with cores consisting of bundles of axis cylinders were observed, and the tumor cells containing numerous fine granules resembled Schwann cells in experimental wallerian degeneration [13, 14] and the tumor cells of schwannoma (Antoni B type) [20]. The other proposed progenitor cells of granular cell tumors are undifferentiated mesenchymal cells [18, 19]. EVERSOLE et al. [23] believed that the varied light and electron microscopic features of granular cell tumors could not possibly have substantiated a single specific progenitor cell in three cases and they proposed the term “granular sheath lesion” for this tumor. Other investigators also believe that this lesion does not arise from a single cell type [21,22,24,25]. In our present case the relationship to nerve fibers and the existence of axon were not observed, but the tumor cells resembled Schwann cells in view of electron microscopic observations where the nuclei and cell membrane, completely coated by basement membrane, were invaginated in places and microfilaments were observed in the cytoplasm. There were many small and large unit membrane-delimited bodies in the cytoplasm of the tumor cells. These were secondary lysosomes which resembled autophagic vacuoles and the tumor cells were negative for myoglobin.

We believe that these tumor cells are derived from Schwann cells and represent a peculiar degenerative change. Undifferentiated mesenchymal cells were also observed in the stroma, but any evidence that the tumor cells were derived from these cells was not recognized.

In the stroma of this tumor lymphocyte-fibroblast interactions, regarded as cellular cytotoxicity, were often observed. This cellular cytotoxicity, in response to some unknown stimulus, may occur as a pseudoepitheliomatous hyperplasia of the surface epithelium and prevent the formation of a capsule.

**Conclusion**

A case of a 38-year-old female with a granular cell tumor on the right border
of her tongue was described. Light and electron microscopic examinations showed a typical granular cell tumor. In view of the morphological observations of the present case we think that the present case was derived from Schwann cells. Further, the cellular cytotoxicity observed as a lymphocyte-fibroblast interaction in the stroma of this tumor may occur as a pseudoepitheliomatous hyperplasia of the overlying epithelium and prevent the formation of a capsule.

References


