CASE REPORT

Neural granular cell tumor. A case report

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Abstract

It is presented the case of an old female with a solitary tumor at the level of the thorax. The specimen was processed using the routine histological technique and slides were stained with conventional morphologic, histochemical and immunohistochemical methods. On Hematoxylin–Eosin stained slides were noticed large cells with acidophilic cytoplasm, with granular pattern. S100 protein was intensely expressed in all tumor cells and neuron specific enolase was moderate positive. CD68 positive reaction was considered the expression of lysosomes accumulation in the cytoplasm of tumor cells. Histological and immunohistochemical findings are consistent with the diagnosis of neural granular cell tumor.

***Keywords*:** granular cell tumor (GCT), Schwann cells, immunohistochemistry, S100 protein.

Introduction

Granular cell tumor is a rare, usually benign lesion that may occur at any age, race, and sex, and is more frequent between the 4th and the 6th decade in female (rate female/male 3 : 2) and Africans. This tumor is also known as myoblastoma with granular cells, schwannoma with granular cells, and neurofibroma with granular cells, granular neurogenic tumor, or Abrikosoff tumor. The malignant variant of this tumor means only 1–2% from all granular cell tumors, it has a fatal outcome, and until now, there where described such cases only in adults [1, 2].

Granular cell tumor is usually a solitary tumor, the most frequent sites being the skin (43%, mainly the anterior and posterior thorax and upper limb) and the tongue (23–40%). In the literature there are also reported other locations, as bronchi, larynx, esophagus, stomach, vermiform appendix, rectum, anal canal, biliary ducts, pancreas, uveal tract, urinary bladder, uterus, brain, hypophysis and mammary gland [3, 4]. Multiple tumors were reported in 5 to 25% of cases and this form is rarely found in children. In 1990, Martin *et al.*, cited by [2] published a study on 26 cases of multiple tumors in children and teenagers, and all had benign features. One patient from this series developed during the adult life a corresponding malignant tumor. There were also reported few congenital cases, located especially at the level of the gingival, and some of them with systemic involvement [5].

Patient and methods

A 75-years-old female was admitted with the clinical diagnosis of cutaneous fibroma. The clinical examination showed a cutaneous tumor on the anterior side of the thorax, 2.5/3 cm in size, without significant changes of the surface of the skin. The patient accused mild pain at pressure. The tumor was completely removed by surgery and the macroscopic examination showed a tumor located in the dermis, firm, with ill-defined borders, white-grayish in color with some yellow striations.

The specimen was fixed in 10% buffer formalin and paraffin-embedded, using the standard histological procedure. Step section 5 μm thick were stained with routine morphologic methods (Hematoxylin–Eosin, Masson's trichrome), histochemical methods (PAS reaction, Gordon–Sweet silver staining, and orcein), and immunohistochemical reactions for S100 protein (polyclonal), neuron specific enolase, vimentin (clone V9), smooth muscle cell actin (clone 1A4), CD68, and polyclonal cytokeratin MNF116. The working system was LSAB2, DAB was used as chromogen, and nuclei were stained with Lillie's modified Hematoxylin.

Results

Microscopic examination showed a proliferation with tumor cells arranged in cords and nests, separated by bundles of collagen fibers (Figure 1a). The tumor was predominantly localized in the deep dermis, and extensions with tumor cells were also noticed in the connective septa between the adipose lobes of the subcutaneous tissue. Tumor cells were round or ovoid in shape, with well-defined borders, alternating with areas containing cells with ill-defined borders. The cytoplasm of tumor cells contained numerous acidophilic, small and relatively equal granules. Occasionally, there were observed homogenous large granules surrounded by a thin pale stained rim (Figure 1, b and c). Nuclei of tumor cells were round or ovoid in shape, centrally or eccentrically, often with prominent nucleoli and without mitotic activity. All granules were PAS positive, with moderate intensity (Figure 1d). Any particular aspect

was found on slides stained for elastic and reticular fibers.

The immunohistochemical profile was consistent with a granular cell tumor. We found an intense positive reaction for S100 protein (Figure 2, a and b), vimentin, neuron specific enolase (Figure 3a), and just a weak reaction with CD68 (Figure 3b). Immunoreactions for smooth muscle cell actin and cytokeratin were negative.

Discussions

Granular cell tumor (GCT) was first described in 1854 by Weber, as a tumor of the tongue in a young man; the tumor consisted of tumor cells with granular acidophilic cytoplasm. Later, Abrikosoff in 1926, reported many tumors with granular cells in the muscle tissue, which he called myoblastic myoma; this name was given because the possible origin of the tumor from striated skeletal cells [2]. Many years from these findings, GCT was known in the literature as granular cell myoblastoma that suggested the origin of tumor cells in myoblasts.

Electron microscopy data showed some similar aspects between tumor cells of GCT and Schwann cells (as they look during wallerian degeneration), and they support the neural origin of the tumor. Both cells contain inclusions that are similar to myelin, they are surrounded by a basal lamina, and within the tumor are found non-myelinated nerve fibers and structures that are similar with degenerated nerve fibers [5]. Moreover, both tumor cells and Schwann cells do express S100 protein. The immunohistochemical profile is confirmed by our observations, and we found a strong and homogeneous positive reaction for S100 protein and a moderate positive reaction for neuron specific enolase in all tumor cells. Because of these reasons, nowadays it is accepted that granular cells arise from Schwann cells. Somehow, surprisingly, present data confirm the old hypothesis of Freyter from 1935 (cited by [6]).

Although the large majority of GCTs do express S100 protein, it still remains a group of tumors that have not a specific morphologic and immunohistochemical profile. The most important aspect that discriminates between these two types is the expression of S100 protein: the neural type (that arises from Schwann cells) is S100 protein positive, and the non-neural type, which is negative for the same marker. The non-neural type was first described by Le Boit P *et al.* [7] as a primary polypoid tumor with granular cells, associated with negative reaction for S100 protein.

Neural GCT is usually a solitary nodular tumor, rarely found in children. The tumor is small (less than 3 cm), but on occasion, there were reported large tumors, up to 10 cm [1]. The tumor is firm, with ill-defined borders, and on the cut surface is white-yellowish. Large tumors are sometime ulcerated, and this explains why the clinical examinations could create confusion with a malignant proliferation. Some neural GCT can induce changes of the skin surface, as hyperplasia of the epidermis that may lead to errors in the microscopic diagnosis, mainly in small superficial biopsies. The tumor is located mainly in the deep dermis and extended to the subcutaneous tissue, containing cells arranged in cords and nests, which was also noticed in our case.

Opposite to the neural GCT, the non-neural type is usually polypoid, more frequently found in the 3rd decade, with mild female predominance. The mean age is around 33 years but limits are very large (between 5 and 83-years-old) [7–9]. The lesion is painless, popular-nodular or polypoid, less than 1.5 cm and can be ulcerated. The typical location is at the level of the limbs, head and neck. Lazar AJF and Fletcher CDM [9] reported such a tumor on the posterior side of the thorax. The proliferation is usually restricted to the papillary dermis, with well-defined borders, and just rarely extending to the deep dermis. This tumor is not associated with hyperplasia of the epidermis (or this change is minimal) [8].

In neural GCT, tumor cells are round of oval in shape, with granular, intense acidophilic cytoplasm and large inclusions surrounded by a clear thin rim, as we shoed in our case. Data from electron microscopy demonstrated that acidophilic granules are secondary lysosomes, and were confirmed by immunohisto-chemistry, which showed a positive reaction for CD68, as it was done in our study. CD68 positive reaction is attributed to the cytoplasmic accumulation of lysosomes, and this aspect does not reflect the histiocytic nature of the proliferation [1].

In non-neural GCT, tumor cells are spindle, round or polygonal in shape, with intensely granular cytoplasm. Two histological aspects should be taken into account: presence of atypical cells and an increased mitotic activity. In the large majority of cases, nuclear atypia is moderate with focal distribution, with intensely stained nuclei and small acidophilic nucleoli. Mitoses are more or less frequent, vary rare in some cases, and about 4/low power field in others. It has to be mentioned that these features are not indicators of the local recurrence rate or of the metastatic potential [8].

The malignant variant of neural GCT is rare. Reed RJ and Argenyi Z [10] mention two types of malignant GCT, characterized by particular histological aspects. The first type, although it looks clinically like a malignant tumor, in microscopy shows similar features with a benign GCT tumor, excepting for some mitotic figures, mild atypia, and a little bit more larger nuclei [11, 12]. These cellular characters are too common to be enough for the diagnosis of malignancy. This is why in such a case the final diagnosis is based in part on the clinical data, ulceration and invasion. The mean size of this tumor is about 9 cm, significantly higher than in the benign counterpart (less than 3 cm). All these clinical data are thought to be more valuable for the diagnosis than histological features. The second subtype of malignant GCT consists of pleomorphic granular cells, spindle cells without granules, giant non-granular cells and many mitotic figures [13].

Cytological criteria proposed by Enzinger for the diagnosis of malignant GCT include vesicular nuclei with prominent nucleoli, increased mitotic activity (more than 2 mitotic figures/low power field), increased nuclear cytoplasmic ratio and nuclear pleomorphism.

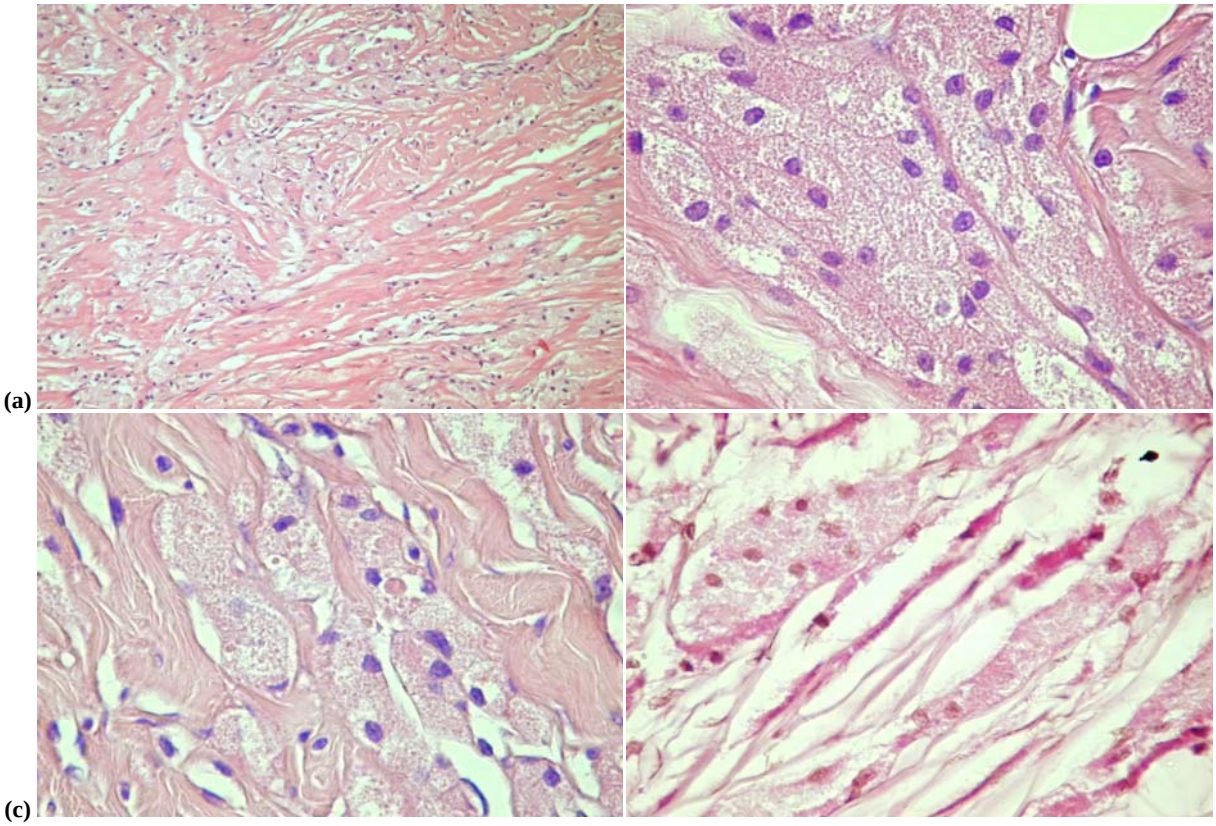

Figure 1 – ***Tumor cells in cords and nests (a – HE stain, ×100). Tumor cells with granular acidophilic cytoplasm (b – HE stain, ×200). Small and large cytoplasm granules (c – HE stain, ×200). PAS-positive reaction in tumor cells (d – PAS stain, ×200)***

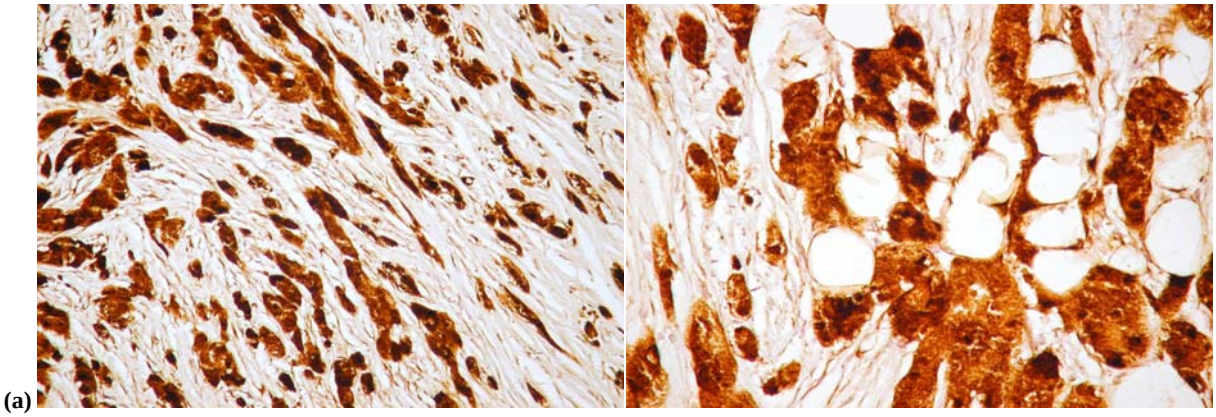

Figure 2 – ***Strong positive reaction in tumor cells (a – S100 protein, ×100), and in neighboring adipose cells (b – S100 protein, ×100)***

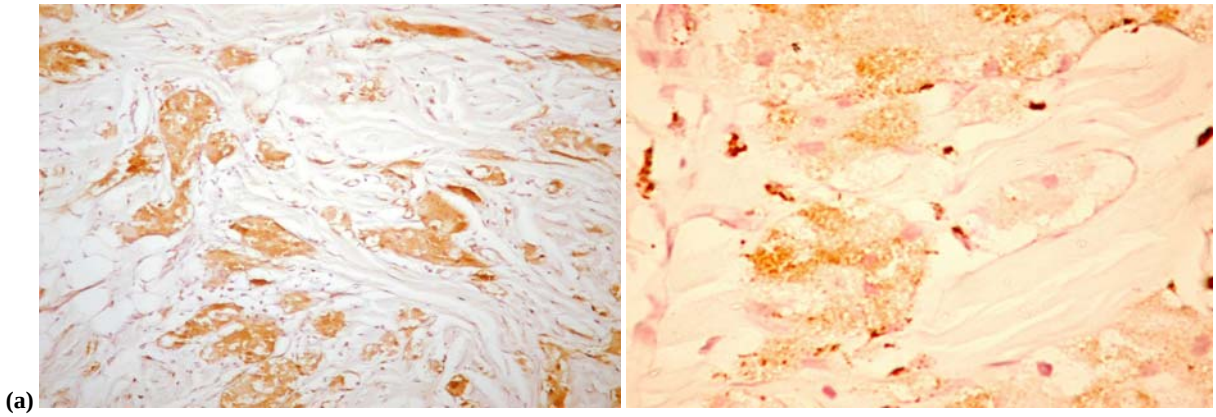

Figure 3 – ***Granular cell tumor. Neuron specific enolase (a, ×100). CD68 (b, ×200)***

Less than three criteria found in a tumor recommend the term "atypical granular cell tumor". It seems that these criteria apply only to neural GCT and not for non-neural type.

Changes in the structure of tumor cells are also found in a large variety of proliferative lesions as melanocytic nevi, rhabdomyoma, dermatofibroma, dermatofibrosarcoma protuberans, basal cell carcinoma, cutaneous angiosarcoma, cutaneous leiomyosarcoma, and others. In these instances, granular cells are found only in restricted areas of the tumor and not in the entire proliferation [8, 14, 15].

Complications of GCT are local recurrences and metastasis. In benign tumors, the rate of recurrence is between 2 and 8%, even when margins of resection are free of tumor. The rate of recurrence rises to 20–50% when margins of resection are not free of tumor. Ki67 is positive in about 10% of cases and is considered an individual prognostic factor that predicts the unfavorable outcome. The malignant variant is aggressive, and metastases are usually found within 2 years from the diagnosis of the primary. Approximately 60% of patients die within 3 years from the diagnosis.

Conclusions

The case report presents a solitary neural granular cell tumor. The histological features of tumor cells, without significant mitotic activity or pleomorphism, with granular acidophilic cytoplasm, and the immunohistochemical profile with S100 protein, neuron specific enolase positive reactions support the diagnosis of a benign tumor. Characterization of this tumor helps to avoid confusion with other tumors of the soft tissues.

References

[1] LE B. H., BOYER P. J., LEWIS J. E., KAPADIA S. B., *Granular cell tumor: immunohistochemical assessment of inhibin-alpha, protein gene product 9.5, S100 protein, CD68, and Ki-67 proliferative index with clinical correlation*, Arch Pathol Lab Med, 2004, 128(7):771–775.

[2] TOMSON N., ABDULLAH A., TAN C. Y., *Multiple granular cell tumors in a child with growth retardation. Report of a case and review of the literature*, Int J Dermatol, 2006, 45(11):1358–1361.

[3] AL-AHMADIE H., HASSELGREN P. O., YASSIN R., MUTEMA G., *Colocalized granular cell tumor and infiltrating ductal carcinoma of the breast a case report and review of the literature*, Arch Pathol Lab Med, 2002, 126(6):731–733.

[4] PARFITT J. R., MCLEAN C. A., JOSEPH M. G., STREUTKER C. J., AL-HADDAD S., DRIMAN D. K., *Granular cell tumours of the gastrointestinal tract: expression of nestin and clinicopathological evaluation of 11 patients*, Histopathology, 2006, 48(4):424–430.

[5] MAIORANO E., FAVIA G., NAPOLI A., RESTA L., RICCO R., VIALE G., ALTINI M., *Cellular heterogeneity of granular cell tumours: a clue to their nature?*, J Oral Pathol Med, 2000, 29(6):284–290.

[6] CHENG S. D., USMANI A. S., DEYOUNG B. R., LY M., PELLEGRINI A. E., *Dermatofibroma-like granular cell tumor*, J Cutan Pathol, 2001, 28(1):49–52.

[7] LEBOIT P. E., BARR R. J., BURALL S., METCALF J. S., YEN T. S., WICK M. R., *Primitive polypoid granular cell tumour and other cutaneous granular cell neoplasms of apparent nonneural origin*, Am J Surg Pathol, 1991, 15(1):48–58.

[8] CHAUDHRY I. H., CALONJE E., *Dermal non-neural granular cell tumour (so-called primitive polypoid granular cell tumour): a distinctive entity further delineated in a clinicopathological study of 11 cases*, Histopathology, 2005, 47(2):179–185.

[9] LAZAR A. J. F., FLETCHER C. D. M., *Cutaneous non-neural granular cell tumours: analysis of ten cases*, Mod Pathol, 2004, 17(Abstr 388):95A.

[10] REED R. J., ARGENYI Z., Tumors of neural tissue. In: ELDER D., ELENITSAS ROSALIE, JAWORSKY CHRISTINE, JOHNSON B. JR. (eds), , *Lever's Histopathology of the Skin*, 8th edition, Lippincott–Raven, Philadelphia, 1997, 993–995.

[11] KLIMA M., PETERS J., *Malignant granular cell tumor*, Arch Pathol Lab Med, 1987, 111(11):1070–1073.

[12] UZOARU I., FIRFER B., RAY V., HUBBARD-SHEPARD M., RHEE H., *Malignant granular cell tumor*, Arch Pathol Lab Med, 1992, 116(2):206–208.

[13] AL-SARRAF M., LOUD A. V., VAITKEVICIUS V. K., *Malignant granular cell tumor: histochemical and electron microscopic study*, Arch Pathol, 1971, 91(6):550–558.

[14] LACROIX-TRIKI M., ROCHAIX P., MARQUES B., COINDRE J. M., VOIGT J. J., *Granular cell tumors of the skin of nonneural origin: report of 8 cases*, Ann Pathol, 1999, 19(2):94–98.

[15] SANZ-TRELLES A., WEIL-LARA B., ACEDO-RODRIGUEZ C., *Dermatofibroma with granular cells*, Histopathology, 1997, 30(5):495–497.

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