

CASE REPORT

Multiple granular cell tumors with metachronous occurrence in tongue and vulva. Clinicopathological and immunohistochemical study

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Received: 09-01-2013

Accepted: 08-01-2015

ABSTRACT

Granular cell tumor (GCT) usually occurs as a single tumor, although sometimes multiple lesions can occur. In present report we analyze the clinicopathological and immunohistochemical features of a multiple GCT involving the tongue of a 14-year-old girl, with no other abnormalities, with a metachronous occurrence of a second GCT in vulva, after a period of 10 years. Both tumors revealed S-100, vimentin and CD57 positivity. In addition, over expression of calretinin was observed in tumor cells located in the vicinity of pseudoepitheliomatous hyperplasia (PEH) of the tongue. Tumor vasculature situated close to the PEH showed marked CD105 reactivity, data not described so far, suggesting an interaction between PEH cells and underlying stroma, since GCT completely lacks CD105 vessels. Our study emphasizes that patients with GCT, especially young patients, should be followed long-term, looking for multiple tumors or other abnormalities suggestive of a systemic syndrome, given the associations described in multiple GCT.

Key words: Multiple granular cell tumors, pseudoepitheliomatous hyperplasia, tongue

INTRODUCTION

Granular cell tumor (GCT), also known as Abrikossoff's tumor, is a rare benign soft tissue neoplasm that most often arises in the tongue,^[1] and also occurs in other anatomic locations, including the vulva. GCT was originally described by Abrikossoff in 1926 in a patient with a tongue lesion and because of the apparent association between granular tumor cells and skeletal muscle the term "granular cell myoblastoma" was proposed in the original description. However, it is now commonly accepted that GCT is of neural origin and most likely derived from Schwann cells, a pathogenesis suggested by immunohistochemical and ultrastructural studies,^[2] although some authors believe that GCT is not a specific entity, but rather a degenerative change that can occur not only in Schwann cells, but also in a variety of other neoplastic cells.^[3]

GCT usually occurs as a single tumor, frequently in the head and neck region especially in the tongue, nevertheless multiple lesions occur in 7–29% of cases.^[1,4] Multiple GCTs most often appear in black women, frequently including intraoral GCT, having either a synchronous appearance or presenting as a sequential development over time.^[4]

In the present study we report a case of a GCT involving the tongue of a 14-year-old girl, with no other abnormalities and with a metachronous occurrence of a second GCT in vulva, after a period of 10 years. Both tumors were analyzed by optical microscopy and immunohistochemistry and several observations were made regarding their presentation and immunohistochemical profile.

CASE REPORT

In November 2001, a 14-year-old Caucasian girl presented with a painless lingual swelling, incidentally discovered 4 months earlier. The patient had no lingual bleeding or previous trauma of the tongue. There was no previous clinical history of interest, the patient referred a healthy lifestyle, had no family history of tumors and all laboratory data were normal. Oral examination revealed a single, firm nodule about 2 cm in size on the left side of the dorsum of the tongue, with a smooth surface and a slight yellowish color. The

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10.4103/0973-029X.151343

lesion was apparently indolent and not ulcerated; there were no palpable lateral cervical lymph nodes. Excisional biopsy was performed, which revealed histopathological features consistent with a GCT associated with pseudoepitheliomatous hyperplasia (PEH) of lingual epithelium [Figure 1 and 2]. The deep resected margin was affected by the tumor; therefore, a clinical follow-up was planned at 1, 6, 12, 24 and 36 months after surgical excision. There were no signs of tumor recurrence during the postoperative follow-up period.

Ten years later, in September 2010, at 24 years of age, the patient was seen again by the Gynecology Service for a single vulvar nodule, slightly painful on palpation, associated with pruritus. At this time no other abnormality was detected clinically or radiologically after a full medical checkup. Gynecological examination was unremarkable, except for the finding of a subcutaneous 1.5 cm mobile nodule in the skin of the left labium minus, which was preoperatively interpreted as a vulvar sebaceous cyst. In lithotomy position, the vulvar nodule

was resected via a longitudinal incision with decapsulation of the nodule together with a small portion of vulvar skin. Histopathological examination revealed the presence of a GCT [Figure 3] without PEH in the overlying vulvar mucosa and with no cytologic features of atypia or malignancy. The margins of the specimen were involved, but no reexcision was performed. At present the patient remains free of vulvar tumor recurrence after 15 postoperative months. A prolonged clinical follow-up is planned for the patient.

Histologically, both lingual and vulvar lesions were composed of cells with large eosinophilic and granular cytoplasm, presenting small central nuclei and intracytoplasmic PAS-positive granules [Figure 4]. No atypical mitoses, pleomorphism or necrosis were observed in either lesion and both showed involvement of the deep resected edge. Nevertheless, there were some distinct features between the two lesions. In the lingual lesion, the tumor cells were intermingled in the deep areas with bundles of striated muscle [Figure 5] and arranged in nests and sheets of variable size.

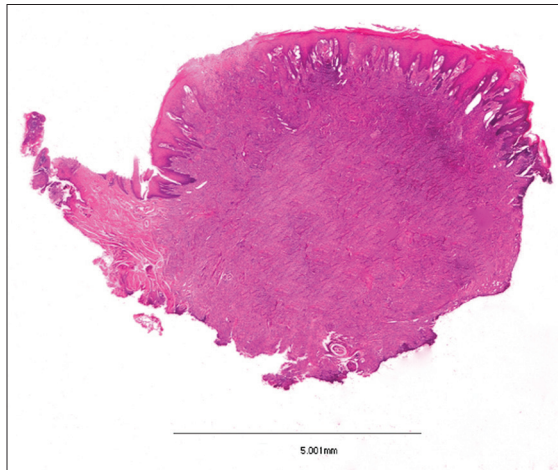


Figure 1: Photomicrograph of the lingual lesion showing overlying surface epithelium with cellular underlying connective tissue (H&E stain, x10)

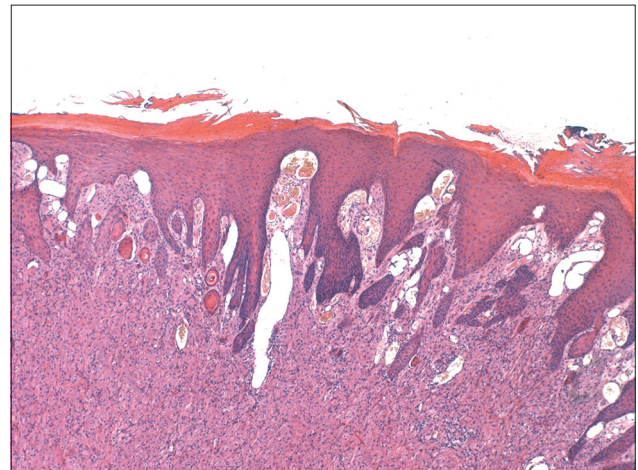


Figure 2: The surface epithelium of lingual GCT shows pseudoepitheliomatous hyperplasia (PEH) (H&E stain, x100)

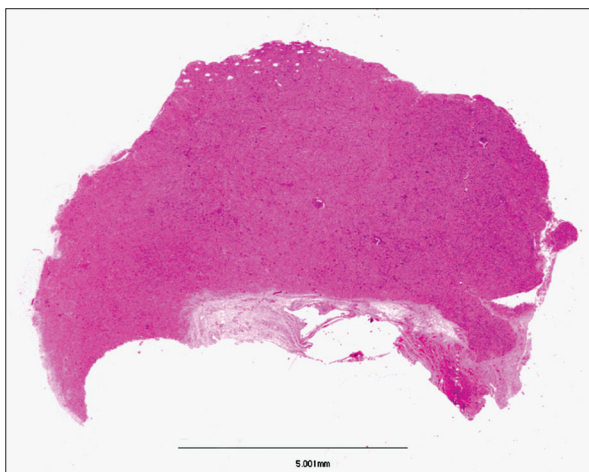


Figure 3: Photomicrograph of the vulvar lesion diagnosed with an interval of 10 years showing a cellular tumor (H&E stain, x10)

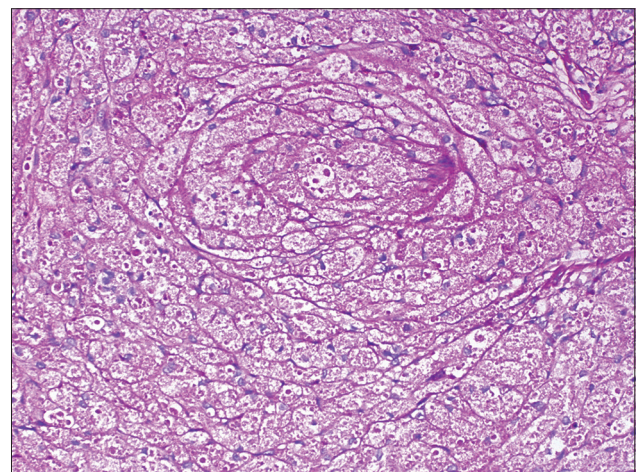


Figure 4: Tumor cells showed a periodic acid Schiff (PAS) positive granular cytoplasm (PAS stain, x400)

These characteristics were absent in the vulvar tumor that showed a nodular growth pattern with expansive outline. PEH was observed only in the tumor of the tongue.

The immunohistochemical study revealed strong positivity (+++) of the tumor cells of both lesions for S-100 protein (cytoplasmic and nuclear staining; polyclonal rabbit antibody, Ready to Use (RtU); Dako, Glostrup, Denmark) [Figure 6], vimentin (predominantly membranous pattern; V9 clone, RtU; Dako) [Figure 7] and CD57 (Leu7;TB01 clone, RtU; Dako); and a mild positivity (++) for enolase (ENS; BBS/NC/VI-H14 clone, RtU; Dako), CD68 (KP1 clone, RtU; Dako) and α -inhibin (R1 clone, RtU; Dako); the latter marking about 10% of tumor cells; whereas, pan-cytokeratin (clone AE1/AE3, RtU; Dako), desmin (D33 clone, RtU; Dako), smooth muscle actin (1A4 clone, RtU; Dako), α -estrogen receptor (α -ER; 1D5 clone, RtU; Dako), progesterone receptor (PgR 636 clone, RtU; Dako) and androgen receptor (AR-441 clone, dilution 1:50; Dako) were all negative.

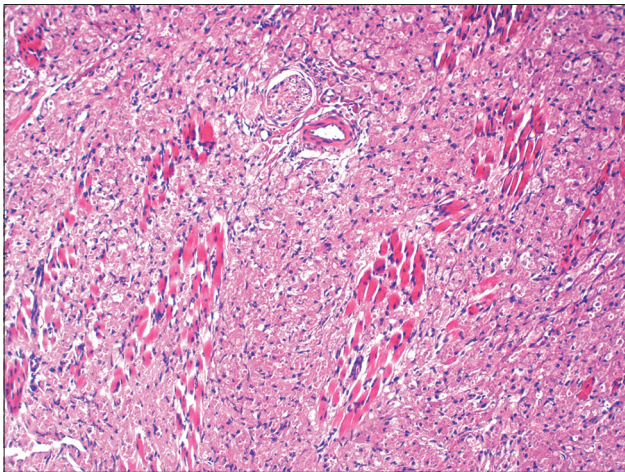


Figure 5: Deep areas of lingual granular cell tumor (GCT) showing tumor cells intermingled with bundles of striated muscles (H&E stain, x200)

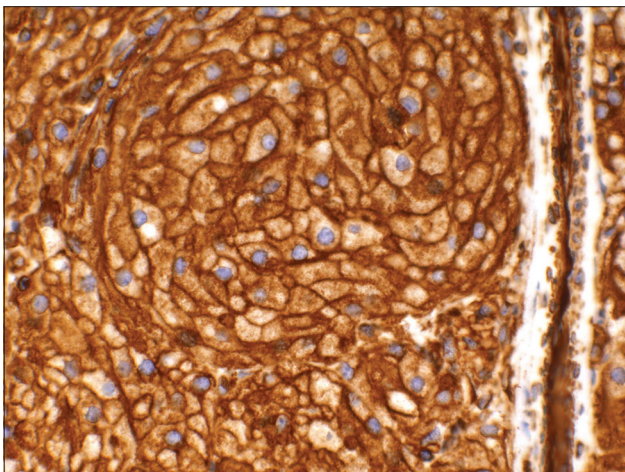


Figure 7: The tumor cells showing intense positivity for vimentin (IHC stain, x400)

In addition, we found only weak positivity (+) for calretinin antibody (polyclonal antibody, dilution 1:30, BioGenex) in the vulvar tumor. However, calretinin was more pronounced (++) in the lingual tumor, particularly in tumor cells located in the vicinity of the overlying PEH [Figure 8] that showed a clear calretinin over expression. Interestingly, tumor vasculature situated close to PEH showed marked CD105 (endoglin; SN6h clone, RtU; Dako) reactivity [Figure 9], while all remaining vessels were negative for endoglin, as was found in all vulvar tumor vessels. Moreover, in both tumors Ki-67 antigen (MIB-1 clone, ready to use; Dako) showed a very low percentage (1–2%) of labeled tumor cell nuclei, nuclear expression of p53 (DO-7 clone, RtU; Dako) being completely negative. In the lingual tumor, areas with PEH showed marked Ki-67 positivity in overlying epithelia [Figure 10], with strong nuclear Ki67 staining in 20–30% of basal and parabasal cells.

DISCUSSION

GCT is an uncommon soft tissue tumor. Although it most

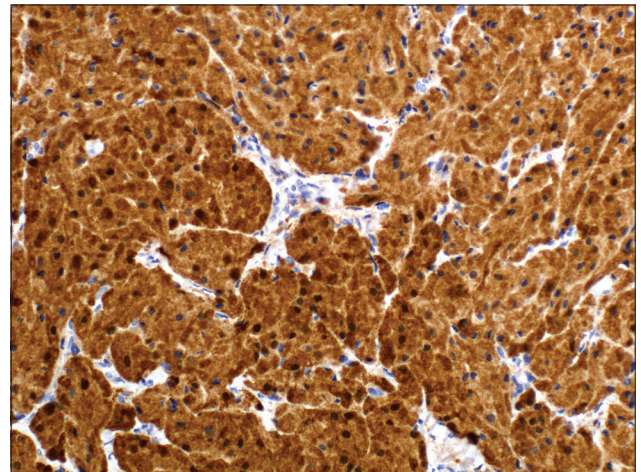


Figure 6: The tumor cells were intensely immunoreactive for S-100 protein (IHC stain, x400)

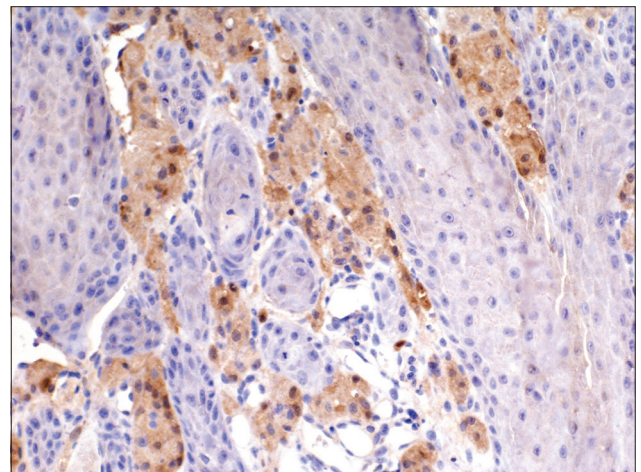


Figure 8: GCT in close contact with PEH displayed overexpression of calretinin protein (IHC stain, x250)

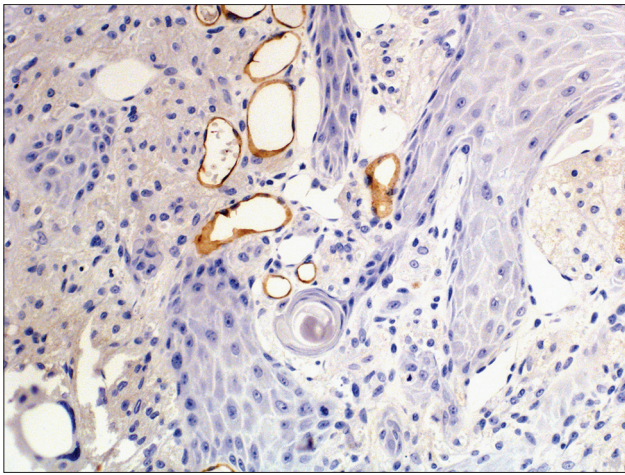


Figure 9: The tumor cells close to the epithelium of lingual tumor were associated with a CD 105 positivity in the vascular network unlike the remaining vessels that were negative for endoglin ie CD 105 (IHC stain, x400)

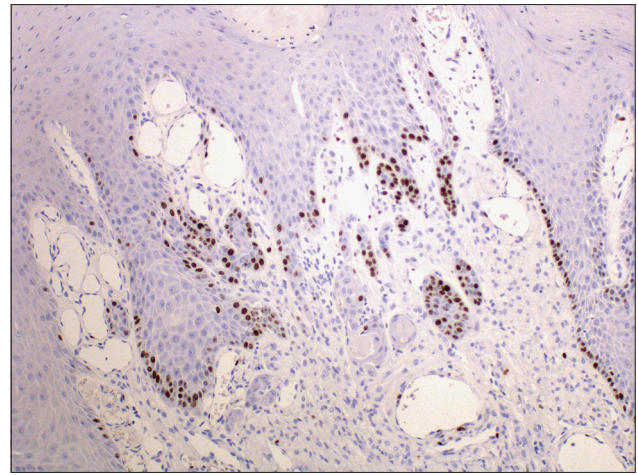


Figure 10: Isolated tumor cells were positive for Ki67 whereas the overlying PEH epithelium of the lingual tumor showed marked Ki67 activity (IHC stain, x250)

frequently involves the head and neck region, especially the tongue which represents approximately 30% of lesions,^[1] it has been found throughout the body. GCT is seen almost invariably as a benign tumor, usually solitary, although very uncommon malignant GCTs have also been described^[5] and multiple benign GCT lesions can occur in up to approximately 25% of cases, suggesting that a patient with GCT should undergo a complete physical examination, given that the presence of another tumor is quite possible and certainly more common than is generally thought.

Multiple GCTs are most often located in the intradermal or subcutaneous tissue, although oral mucosa, gastrointestinal and genital tract^[4] can also be involved, with a synchronous or metachronous occurrence, as was presented by our patient with an interval of 10 years between the two tumors. Nevertheless, the cases of concurrent presentation seem to be more frequently reported in the literature.^[4]

Clinically, our patient presented no other abnormality and had no family history of GCT, all exploratory data being completely normal after a full medical checkup. This is important since in the last decade multiple GCT have been described in association with syndromes, such as LEOPARD syndrome and Noonan syndrome, as well as with neurofibromatosis type I.^[6,7] Curiously, in all these processes there is an aberrant signaling in the Ras/MAP pathway, which promotes cellular differentiation, proliferation and oncogenesis, with a special vulnerability in Schwann cells, the putative origin of GCT. Given these associations, it has been suggested that a diagnosis of multiple GCT, especially in young patients as in this case warrants a complete physical examination, for systemic manifestations of underlying genetic or somatic defects.^[7] So the take-home message, given these data and the potential multicentricity of GCT,^[1,4] would be that in the presence of a diagnosis of GCT in a young patient a complete physical

examination in search of other possible tumors or coexisting abnormalities is obligatory, as well as planning a prolonged clinical follow-up, as highlighted by the present case is also necessary.

In our patient both GCT were studied with a broad panel of antibodies and our immunohistochemical findings being generally in agreement with those reported in the literature.^[1,8] In our opinion, the strong positivity found for S-100, vimentin and CD57 point to a possible schwannian/neural origin as the most plausible for these tumors. The low proliferation index with Ki67 and p53 negativity confirm the benign nature of the two CGTs in our patient, which curiously has not recurred despite involvement of the deep rim, an aspect previously reported by others,^[4] indicating that these are slow-growing tumors with a low and late recurrence rate, even with positive margins^[4] and regardless of the pattern of invasion. Absence of hormone receptors (α -ER, PgR and AR) in both tumors in principle excludes the existence of any hormonal influence on their appearance, data that cannot explain the increased incidence of multiple GCT in women.^[4]

Finally with regard to PEH, this morphological change can appear in the overlying epithelium of approximately 50% of GCT,^[2] mimicking squamous cell carcinoma and sometimes posing a challenge for diagnosis. In addition, the cellular component of GCT close to the PEH showed a clear over expression of calretinin, a primarily neuronal protein, in comparison to the deep portions of tumor, suggesting that calretinin overexpression in some way influenced the appearance of PEH, as already noted by others.^[9] We also found that PEH is located in proximity to a localized network of vessels immunoreactive to endoglin, this previously undescribed data suggests, in our opinion, an interaction between PEH cells and underlying stroma since GCT lacks CD105 + vessels. However, a full understanding of the role

of CD105 in the interaction between GCT and hyperplastic squamous epithelium requires further study in a wide series of GCT analyzing what factors trigger the development of PEH in GCT.

CONCLUSION

Our study emphasizes that patients with GCT, especially young patients, should be followed for a long-term, looking for multiple tumors or other abnormalities suggestive of a systemic syndrome, given the associations described in multiple GCT.

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How to cite this article: Vera-Sirera B, Zabala P, Aviño-Mira C, Vera-Sempere FJ. Multiple granular cell tumors with metachronous occurrence in tongue and vulva. Clinicopathological and immunohistochemical study. *J Oral Maxillofac Pathol* 2014;18:437-41.

Source of Support: Nil. **Conflict of Interest:** None declared.