GRANULAR CELL TUMOR OF TONGUE IN A 12 YEAR OLD GIRL: A CASE REPORT & REVIEW OF LITERATURE

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HOW TO CITE THIS ARTICLE:

ABSTRACT: Granular cell tumor (GCT) or Abrikossoff’s tumor, variously termed as myoblastoma, granular cell neurofibroma or granular cell schwannoma, is a rare entity, with a reported prevalence ranging from 0.019% to 0.03% of all human neoplasms. It can occur in any region of the body or soft tissues of any organ. It has been found that GCTs of the oral cavity can occur both in pediatric and advanced age, but their incidence usually peaks between the fourth and the sixth decade, while their occurrence before the age of 20 years is very rare. Here we represent a case of GCT affecting tongue of a 12 year old girl, which is a rare occurrence. Clinical & histopathological features have been discussed, also mentioning presence & distribution of immunohistochemical markers & a brief review of recent literature.

KEYWORDS: Granular cell tumor, Young age, Tongue, Benign tumor.

INTRODUCTION: Granular cell tumor (GCT) or Abrikossoff’s tumor was first described by Russian pathologist Alexei Ivanovich Abrikossoff in 1926 and postulated to be of myogenic origin.[1] It is a rare entity, with a reported prevalence ranging from 0.019% to 0.03% of all human neoplasms.[2] Initially the tumor was termed ‘granular cell myoblastoma’, with its possible origin was proposed to be from skeletal muscle.[3]

Thereafter various theories have been put forward regarding origin of GCT. Its origin remains to be controversial as GCT has been postulated to be arising from fibroblasts, [4] myoblasts, [5] undifferentiated mesenchymal cells, Schwann cells, [6] histiocytes [7] and neural cells. [8] Accordingly it has been variously termed as myoblastoma, granular cell neurofibroma or granular cell schwannoma, by different authors. [9]

It can occur in any region of the body or soft tissues of any organ, as cases have been reported in literature affecting head neck region (tongue, cheek mucosa, palate),[10] skin & subcutaneous tissue, breast parenchyma, rectal mucosa, anus, vulva, esophagus, larynx,[11] parotid gland, eyelid & appendix.[12] GCT typically manifests in adults between the third and the sixth decade, usually showing a benign behavior; women are affected twice as much as men (M/F ratio = 1:2).[13]

The most common sign is the presence of an asymptomatic mass.[12] GCT usually appears as a single lesion, less than 3 cm in size (mean diameter of the tumor 1.2 cm, range 0.2- 3.5 cm have been reported in the series of Lack EE et al),[11] generally pink or occasionally yellowish-white in color. The nodular mass is hard, firm, sessile and covered by intact overlying mucosa.[14] Although benign in nature, malignancy rate has been reported to be 2% of cases, where recurrence or metastasis to regional lymph nodes occurred, despite a benign histological appearance.[15]

In the series of Lack EE et al, tongue was the single most common anatomic site involved, but relatively more GCT (44%) occurred in skin or subcutaneous tissue.[11] It has been found that GCTs of the oral cavity can occur both in pediatric and advanced age, but their incidence usually peaks
between the fourth and the sixth decade,\textsuperscript{[16]} while their occurrence before the age of 20 years is very rare.\textsuperscript{[13]}

Here we represent a case of GCT affecting tongue of a 12 year old girl, which is a very rare occurrence, since these tumors typically manifest in subjects between the third and sixth decade. Clinical & histopathological features have been discussed, also mentioning presence & distribution of immunohistochemical markers & a brief review of recent literature.

**CASE REPORT:** A 12 year old girl presented with a painless swelling over dorsum of tongue for last six months. The swelling was insidious in onset, gradually increasing in size, not associated with any episode of bleeding, but caused slight discomfort during mastication & brushing the teeth. On intra-oral examination a pinkish nodular sessile lesion of gummy consistency was noted over middle third of dorsum of the tongue, close to midline on the right side.

The lesion was covered by intact mucosa similar in texture to adjacent mucosa of rest of the healthy tongue, about 0.5 cm in size & was non-tender to palpation (figure 1). The girl was otherwise healthy without any clinical history of any significant chronic illness (diabetes, hypertension, and allergy) or any history of major illness or hospitalization. The laboratory investigations were unremarkable. We advised the patient to undergo a fine needle aspiration cytology (FNAC) from the lesion, which pointed out a provisional diagnosis of granular cell tumor (GCT) involving the tongue.

We performed a magnetic resonance imaging (MRI) of tongue to get an idea of the depth of the lesion preoperatively. Multi-planar plain & contrast enhanced MRI of tongue & adjacent neck was done by taking T1, T2 & STIR sequences. The imaging study revealed an elliptical mildly enhancing lesion in the right para-median location of dorsum of tongue having predominantly exophytic component, measuring about 9mm (AP) x 8mm (ML) x 7mm (SI) (figure 2). There was a plane of cleavage between the lesion & the overlying mucosa, but the lesion was found to invade superficial part of adjacent tongue substance for a depth of about 6mm (figure 3).

Rest of tongue substance & tongue musculature was normal in terms of signal intensity & contrast enhancement pattern & there was no significant cervical lymphadenopathy. With this background, we planned for surgical excision of the tongue mass under general anesthesia. The patient underwent endotracheal intubation & the tongue mass was excised completely with hemostasis achieved using bipolar diathermy (figure 4). The excised specimen measured about 9x7x5mm, well circumscribed nodule, pale pink to whitish in color (figure 5).

The specimen was fixed in 10% buffered formalin and embedded in paraffin. 4 µm histological sections from the paraffin-embedded block were stained using haematoxylin-eosin. On histopathological examination the lingual epithelium showed marked pseudoepitheliomatous hyperplasia, while in the underlying submucosa a neoplastic proliferation was observed. Sheets of large polygonal to oval cells with abundant, eosinophilic, granular cytoplasm and poorly defined cellular borders imparting a syncytial growth pattern were present (Hematoxylin & eosin stain;10X) (figure 6).

Under higher magnification, sheets of large polygonal to oval cells with abundant, eosinophilic, granular cytoplasm; small vesicular eccentric nucleus & poorly defined cell borders were noted (Hematoxylin & eosin stain; 40X) (figure 7). Immunohistochemical study was performed on the tissue specimen. All the cells were S-100 positive (Company- DAKOCYTOMATION, clone-polyclonal) & intracytoplasmic PAS (para-amino salicylic acid) positive granules were found.
Moderate cytoplasmic staining of inhibin alpha (Company- Lab Vision, clone- R1) (figure 8) was present. Protein gene product 9.5(PGP 9.5, Company- Leica, clone- 10A1) reaction showed diffuse nuclear & cytoplasmic staining of PGP 9.5 (figure 9). Moreover diffuse intense cytoplasmic staining of CD 68 (Company- DAKOCYTOMATION, clone- PGM1) was noted (figure 10). On the other hand the cells were immuno negative for Cytokeratin (figure 11). Surgical margins were negative.

Thus all histomorphological and immunohistochemical findings were consistent with GCT of the tongue. The patient was first examined one week later and then, respectively, 1, 3 & 6 months after the surgical excision; so far, no sign of recurrence has been noted. Close follow-up has been planned to assess the effectiveness of the eradication and to prevent any possible relapse of the disease.

**DISCUSSION:** GCT is a relatively uncommon benign neoplasm that occurs in almost any part of the body.[9] In about 45 to 65% of the patients, the head and neck region involved & in 70% of these, the presentation was intra oral lesions. The tongue, buccal mucosa, hard palate are the most frequent oro-facial localisation.[17] In children most of these lesions arise in the cervico-facial region (up to 50% of GCTs occur in the head and neck,[18] only a few cases have been reported in the oral cavity.[19]

The other head and neck site likely to be involved is the larynx (uncommon -6-10 % of reported cases).[20,21] The tumor is rare in children.[9] There are only few studies, those describe the occurrence in the childhood. Here is a summary of the available recent English literature in PubMed search describing GCT involving tongue & oral cavity in younger age group:

<table>
<thead>
<tr>
<th>Name of Authors</th>
<th>Name of Journal</th>
<th>Age of the case &amp; site</th>
<th>Year of Publication</th>
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<tbody>
<tr>
<td>Ozer E et al[22]</td>
<td>Kulak Burun Bogaz Ihtis Derg.</td>
<td>2.5 years-tongue</td>
<td>2004</td>
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<tr>
<td>Pino RV et al[24]</td>
<td>An Otorrinolaringol Ibero Am.</td>
<td>18 years-tongue</td>
<td>2005</td>
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<tr>
<td>Barbieri M et al[27]</td>
<td>Acta Otorhinolaryngol Ital.</td>
<td>14 years-tongue</td>
<td>2011</td>
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<tr>
<td>Russo LL et al[9]</td>
<td>The Open Otorhinolaryngology Journal</td>
<td>8 years Tongue</td>
<td>2011</td>
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<tr>
<td>Suchitra G et al[28]</td>
<td>J Oral Maxillofac Pathol.</td>
<td>9years-tongue</td>
<td>2014</td>
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<tr>
<td>Kaustuv Das Biswas et al</td>
<td>Present case</td>
<td>12years- tongue</td>
<td>2014</td>
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</table>
The etiology of GCT is unclear and there are several hypotheses concerning the histogenesis of GCT.[29] Myoblasts, Schwann cells, histiocytes, perineural fibroblasts and undifferentiated mesenchymal cells have been postulated as the origin of the tumor.[30] Alternatively theories for a non-neoplastic nature of the lesion resulting from trauma, a degenerative process or a storage disorder involving histiocytes have been also proposed.[31]

GCTs are unusual in the first and second decade, therefore, many other benign lesions should be considered in the differential diagnosis: amongst which, minor salivary gland tumors (pleomorphic salivary adenoma), dermoid cysts, vascular lesions, lipomas, benign mesenchymal neoplasm, neuroma, neurofibroma and traumatic fibroma.[25]

Moreover, several malignancies, such as squamous carcinoma and malignant melanoma, should be ruled out, as GCT presenting as uncapsulated, as a pseudo-invasive lesion may mimic these lesions.[32]

It has to be kept in mind that, in the overlying lingual epithelium various degrees of pseudo-epitheliomatous hyperplasia are frequently seen, and this can mimic squamous cell carcinoma; therefore, if incisional biopsy is performed, it should be deep enough to include underlying infiltrating granular cells,[18] or otherwise FNAC followed by complete excision biopsy would be a better choice for diagnosis as well as treatment & is curative in majority of cases. This has been done in our case & the pseudo-epitheliomatous hyperplasia of the overlying mucosa was also found to be present.

On histological examination, GCT typically shows small nests and sheets of polygonal cells with small vesicular nuclei and granular eosinophilic cytoplasm, which is due to intracytoplasmic accumulation of lysosomes and appears to be the main morphological feature of GCTs, better seen in PAS-stained slides.[33]

The same histological features were present in the excised specimen in the case under discussion. Another peculiar finding is immunohistochemical localisation of neuron specific enolase and S-100 protein markers in the tumor cells, that suggests a neural origin of the tumor.[34] Some authors support a peripheral nerve-related cells origin for the majority of GCTs based on the finding of cytoplasmic granules with numerous membrane-bound vacuoles (which contain myelin-like tubules) and indicating some relationships with pre-existent axons.[30,35,36]

It is also to be remembered that granular cell populations have been described in some non-neural neoplasms of the oral cavity such as ameloblastoma, ameloblastic fibroma, odontogenic fibroma, odontogenic cysts, and oral lichen planus.[37,38]

Although these tumors are S100-negative, in contrast to the classic GCT.[39] Another rare and recently described entity, which has common histological features with GCT, is congenital granular cell lesion (CGCL), also known as congenital granular cell epulis or congenital granular cell tumor. Differential diagnosis between GCT and CGCL can be made by immunohistochemical staining for S-100, that is negative in CGCL and positive in GCT.[26]

Vered et al recently tested an extensive panel of antibodies to determine the true origin of this tumor. Granular cells were strongly and diffusely positive for p75, vimentin, calretinin, NKI/C3, inhibin-alpha, protein gene product 9.5 (PGP9.5), and protein S-100. However, the authors mentioned the fact that the antibodies stained different tissues & as a result, no particular cell type that would be responsible for the histogenetic origin of GCT could be identified.[40] In our case immunohistochemical study revealed features in favor of GCT.
The majority of GCTs are benign in nature; thus, the treatment of choice is the conservative surgical excision of the lesion,\(^1\) while the use of adjuvant radiotherapy is controversial. The potential aggressiveness of this tumor should always be borne in mind, as 1-3% of GCTs can present in a malignant way.\(^2\) If surgical removal is correctly carried out, with margins of excision adequately positioned in clinically uninvolved healthy tissue, the prognosis is good, as most of the GCTs have slow growth and lack of aggressive potential.

Since the GCT has a poorly defined margin it is suggested that the tumor should be excised along with portions of adjacent unaffected tissue,\(^6\) although this is not always possible because the tumor lacks a capsule, a condition histologically demonstrated by an undefined cell margin.\(^3\) On review of literature cases of malignant GCT have been found to be reported, including patients with more than one histological type of malignant GCT,\(^4,5\)

Benign GCT of the tongue has been recently reported to coexist with squamous cell carcinoma at the same site.\(^6\) Factors like tumor size, symptoms, rapid progression, invasion of adjacent structures, and the presence of regional and distant metastases are to be considered along-with the histopathological diagnosis of benign or malignant GCT.\(^4,6\)

Histological malignancy should be suggested by the presence of 3 or more of the following 6 criteria: 1) high mitotic activity (> 2 mitoses/10 fields at 200× magnification); 2) necrosis; 3) high nuclear-cytoplasmic ratio; 4) spindling; 5) vesicular nuclei with large nucleoli; and 6) pleomorphism. Neoplasms featuring only one or two of the above-mentioned should be diagnosed as "atypical" GCT.\(^5\) In suspicious or frankly malignant cases, accurate histological examination should include the assessment of proliferation markers, with particular regard to the Ki67-labelling index. In malignant GCTs, the Ki67-index is usually > 10%\(^5\) & it is an important prognostic factor.\(^7\)

It should be always kept in mind that a definitive diagnosis of GCT can only be made following accurate histological examination, and that the risk of recurrence is strongly influenced by the status of the surgical margins.\(^1,6\) In the case under consideration excision was carried out with a margin of healthy tissue, the surgical margins were histologically negative & none of the ominous factors was present. None of the histological features suggestive of malignancy was present in our case. Following surgery, long-term follow-up of the patient should be started, because of the risk of local or distant recurrence even several years after surgery.\(^8\)

The recurrence rate is very variable, ranging from 2-50%, depending on surgical radicality and on the presence of infiltrative growth pattern.\(^8\) In 15% of cases, local relapse is possible because of incomplete excision of the tumor, whereas recurrence occurs in 1% to 3% of cases even after complete removal.\(^9\) Thus, a strict follow up is recommended in all cases to rule out relapses early, being able to treat relapses timely and to check for malignant transformation. Our case seems to turn out as a benign case of GCT occurring in childhood as there has been no evidence of relapse in our case till date.

**CONCLUSION:** Although rare, GCT should be considered in the differential diagnosis of oral lesions, particularly when they are located in the tongue. Differential diagnosis between GCT and several other benign and malignant neoplasms, showing granular cell features, is extremely important with regard to treatment and prognosis.\(^5\)

Every oral lesion of unknown nature should undergo examination and/ or appropriate imaging to reveal the nature and clinical extension of the disease, and then, when feasible, should be
surgically removed. Surgical removal should be wide enough to ensure oncological safety margins and accurate histological examination of the specimen; when granular cells are seen on histology, an appropriate immunohistochemical panel should be applied in order to assess the histological derivation and proliferative index of the tumor. When GCT is diagnosed, close follow-up should be planned in order to prevent any relapse or treat them appropriately.

REFERENCES:

Figure 1: Clinical photograph showing the lesion over middle third of dorsum of the tongue, close to midline on the right side.
Figure 2: T1 weighted MRI (axial section) showing elliptical mildly enhancing lesion in the right para-median location of dorsum of tongue.

Figure 3: T1 weighted MRI (para-sagittal section) showing plane of cleavage between the lesion & the overlying mucosa.

Figure 4: showing the surgical excision site immediately post-operative after achieving hemostasis.
Figure 5: showing the excised specimen, pale pink to whitish in colour.

Figure 6: photomicrograph showing sheets of large polygonal to oval cells with abundant, eosinophilic, granular cytoplasm and poorly defined cellular borders (syncytial growth pattern) (Hematoxylin & eosin stain, 10X).

Figure 7: photomicrograph showing sheets of large polygonal to oval cells with abundant, eosinophilic, granular cytoplasm; small vesicular eccentric nucleus & poorly defined cell borders (Hematoxylin & eosin stain; 40X).
Figure 8: photomicrograph showing moderate cytoplasmic staining of inhibin alpha (40X).

![Fig. 8](image)

Figure 9: photomicrograph showing diffuse nuclear & cytoplasmic staining of PGP 9.5 (40X).

![Fig. 9](image)

Figure 10: photomicrograph showing diffuse intense cytoplasmic staining of CD 68 (40X).

![Fig. 10](image)
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Figure 11: photomicrograph showing tumor cells immunonegative for Cytokeratin (40X).

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