Clinico-Pathological Analysis of Granular Cell Tumor: Study from a Tertiary Care Centre

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ABSTRACT
Background: Granular cell tumor is an uncommon benign tumour mainly occurring in skin, tongue, oral cavity as a solitary nodule. It presents as a painless soft to firm subcutaneous nodule and can be diagnosed after histological examination. It has uncertain histogenesis. Recent ultrastructural stains like S-100, Neuron Specific Enolase have confirmed its derivation from Schwann cells and peripheral nerves.

Material and Methods: This study was conducted in S.C.B. Medical College, Cuttack over a period of two years from January 2015 to December 2016. All the cases presenting as nodules over skin and mucosa subjected to histopathological examination were analysed. Out of these, the cases of granular cell tumors were included in the study. Different variables like age, sex, clinical details, cytology, histopathology and immunohistochemical status were recorded and analysed.

Results: Out of total 206 cases of tumor and tumor like lesions of skin and mucosa, there were total six cases of GCT. The mean age of presentation was 37 years, affecting all male patients and involving different sites of body. All of them were benign without history of recurrence.

Conclusion: This study suggests that GCTs are mostly benign tumors usually affecting males with a prolonged course. Majority of the tumors were positive for S-100 protein supporting the hypothesis of it’s origin from Schwann cells.

Key words: Granular cell tumour, benign, S-100, NSE, AE1, AE2, Schwann cells.

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INTRODUCTION
Granular cell tumour (GCT) is a rare benign tumour and has been a subject of debate over years. Clinically, these tumours are rare and account for approximately 0.5% of all soft tissue tumours.1 Usually granular cell tumours behave in a benign fashion, but they have a tendency to recur. GCTs can affect all parts of the body; however, the head and neck areas are affected 45% to 65% of the time. Of the head and neck cases 70% of lesions are located intraorally (tongue, oral mucosa, hard palate). The next most common location that lesions are found in the head and neck area is the larynx (10%).2 The internal organs involved by GCT are the upper aerodigestive tract. Due to their usually subtle presentation, they are often misdiagnosed, with histological examination setting the correct diagnosis subsequently. Due to it’s infrequent occurrence, literature are scanty except case reports and few small series. We present a series of cases of GCT occurring in various parts of the body with emphasis on its diagnostic approach and immunohistochemical findings.

MATERIALS AND METHODS
The surgical pathology specimens received in Dept. of Pathology, S.C.B. Medical College, Cuttack clinically diagnosed as nodules of skin and mucosa over a period of two years from January 2015 to December 2016 were examined. Those cases diagnosed as of GCT were included in the study and analysed with reference to clinical, biological behaviour and cytological-immunohistochemical features. Clinical details, past history and family history, pre-operative investigation findings like complete blood count were collected and analysed. After examination of cases by cytology and histology, they were subjected to immunohistochemistry with S-100 protein, Neuron specific enolase (NSE), AE1 and AE2.
### Table 1: Clinicopathological parameters in granular cell tumor

<table>
<thead>
<tr>
<th>S. No.</th>
<th>Age &amp; Sex</th>
<th>Location</th>
<th>Duration</th>
<th>Size</th>
<th>Gross</th>
<th>Microscopic findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>17yr</td>
<td>Male</td>
<td>Palate</td>
<td>1 year</td>
<td>3x2cm</td>
<td>Soft swelling over hard palate</td>
</tr>
<tr>
<td>2</td>
<td>45yr</td>
<td>Male</td>
<td>Lumbar region</td>
<td>5 months</td>
<td>5x3cm</td>
<td>Smooth swelling</td>
</tr>
<tr>
<td>3</td>
<td>22yr</td>
<td>Male</td>
<td>Lower lip</td>
<td>3 months</td>
<td>2x1cm</td>
<td>Soft swelling, greyish white on cut section</td>
</tr>
<tr>
<td>4</td>
<td>50yr</td>
<td>Male</td>
<td>Anterior Abdominal wall</td>
<td>15 days</td>
<td>1.5x1cm</td>
<td>Firm subcutaneous nodule, greyish white on cut-section</td>
</tr>
<tr>
<td>5</td>
<td>42yr</td>
<td>Male</td>
<td>Scrotum</td>
<td>1 year</td>
<td>3x2cm</td>
<td>Soft swelling 1.5cm diameter</td>
</tr>
<tr>
<td>6</td>
<td>46yr</td>
<td>Male</td>
<td>Scrotum</td>
<td>8 months</td>
<td>2x2cm</td>
<td>Soft to firm swelling 2.5x2x2cm</td>
</tr>
</tbody>
</table>

**Microscopic findings**

- 1: FNAC-Round cells with eosinophilic granular cytoplasm, ovoid nuclei
- 2: H/P-Neoplastic cells in nests, trabeculae. Large polyhedral cells with abundant eosinophilic granular cytoplasm and round vesicular nuclei and prominent nucleoli.
- 3: FNAC-round to polygonal cells with eosinophilic granular cytoplasm
- 4: H/P- polyhedral to ovoid cells with granular eosinophilic cytoplasm, vesicular nuclei and prominent nucleoli
- 5: FNAC- round to oval cells with eosinophilic granular cytoplasm
- 6: H/P- Polygonal large cells with abundant eosinophilic granular cytoplasm

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**Fig 1:** Clinical photograph of granular cell tumor occurring over posterior part of tongue

**Fig 2:** Gross photograph of GCT showing a skin attached grayish white solid tumor.

**Fig 3a:** Photomicrograph of GCT showing hypertrophied squamous epithelium with tumor tissue arranged in lobules. H&Ex100, (3b): Higher magnification of round to polygonal tumor cells with small vesicular nuclei. H&Ex400
RESULTS
Total number of tumor and tumor like lesions of skin and mucosa were 206. Out of these, soft tissue tumors were maximum with lipoma being the most common entity. This study was based on six consecutive cases of GCT diagnosed during this period of two years. The mean age of patients was 37 years. All the patients were males with involvement of head and neck and other parts of body. (Table 1) There was no involvement of internal organs. The course of the disease was mostly slow, mean period of duration being approximately 7 months. Size of the tumor varied from 1.5x1 to 5x3 cm. (Fig 1) Three of these tumors were diagnosed by fine needle aspiration and others were straight subjected to excisional biopsy and diagnosis as there was no features indicating malignancy in them. Grossly the tumors were solid grayish white and attached to skin in extraoral lesions with smooth surface and without areas of necrosis and haemorrhage. (Fig 2) Histologically the tumor is well circumscribed, arranged in lobules separated by fibroconnective septa with hypertrophy of squamous epithelial lining. (Fig 3a) The cells are round to polygonal containing abundant eosinophilic granular cytoplasm and centrally placed small round vesicular nuclei. (Fig 3b) Immunohistochemical analysis of 4 cases was done, three being positive for S-100 protein (Fig 4a) and one was negative. It was however positive for NSE. (Fig 4b) They were negative for AE1 and AE2. (Fig 5a&b) All the cases of GCTs were benign and treated by excision only and left without any further treatment and with advice for follow up.

DISCUSSION
Granular cell tumor was first reported by Abrikossoff by the name of Granular cell myoblastoma. GCTs are rare benign neoplasms accounting for 0.5% of all soft tissue tumours. They can involve any organ of the body, about 50% of the tumors are found in the head and neck region, most common site being the tongue followed by hard and soft palate. Other locations affected are the breast, the gastrointestinal tract—mainly the lower third of the oesophagus—the respiratory tract, the thyroid gland, the urinary bladder, the central nervous system, and the female genitalia. Regarding the latter, the vulva is the predominant site affected in 5%–16% of these cases, but the disease can also be found in the cervix, the uterus and the ovaries. In our study, 2 cases involved head and neck region, 2 cases were found in scrotum and the other two were found in lumbar region and anterior abdominal wall respectively. It can occur in patients of any age, although it is more common between the fourth and the fifth decades of life, being rare in children. GCT is two or three times more common in women than in men. Black patients are affected more than whites (3:1). The tumor usually presents as a single, firm, painless, small nodule in the submucous tissue, however, multifocal tumors at the first presentation have been reported in 4–10% of cases. Cytological findings diagnosing granular cell tumor have been revealed in few reports after following aspiration from breast, inguinal region and lumbar region. El Aouni et al described the cytological features of GCT of the breast along with similar studies. There was presence of predominantly cellular material composed of both cell clusters and single cells, with abundant amounts of eosinophilic granular cytoplasm and indistinct borders. There were also fairly uniform naked nuclei that were scattered with vacuolated and prominent nucleoli. The nuclei had regular smooth membranes, finely granular and evenly distributed chromatin. In our study, FNAC was done from swellings of palate, anterior abdominal wall and one of the scrotal swellings and our findings were consistent with those of earlier studies.
Histopathologically, in granular cell tumors, the overlying epithelium frequently presents proliferative histological patterns and may or may not be associated with pseudoeppitheliomatous changes. This epithelial pattern can possibly be misunderstood with squamous cell carcinoma, mainly in small fragments of tissue from incisional biopsy. The individual tumour cells are large, polyhedral often present in nests and trabeculae separated by fibrocollagenous septae. The most characteristic feature is presence of eosinophilic granules contained in the cytoplasm of cells. Granularity of the cells in these tumors is due to the accumulation of secondary lysosomes in the cytoplasm. This change is rather nonspecific and can be observed in many non-neural tumors, including those arising from smooth muscle, connective tissue, neurogia, endothelial, and epithelial cells. Since the positive rates for S-100 protein and neuron specific enolase are high, currently it is thought that this tumor originates from Schwann cells. The granules are usually positive for Periodic acid-Schiff (PAS) and Sudan Black but negative for diastase. In our study, biopsy was done for swellings from palate, anterior abdomen wall and lumbar region showing neoplastic cells in nests separated by fibrous septae. The cells were large polygonal, few were polyhedral with abundant eosinophilic granular cytoplasm, round to oval vesicula nuclei and prominent nuclei.

The prognosis of these tumors mainly depends on whether it is benign or malignant. It is generally accepted that benign lesions can be safely managed with local excision on clear margins. Although most of the cases follow a benign course, 1%–2% of GCTs exhibit malignant behaviour and behave like high-grade sarcomas with a high rate of metastases and short survival. By convention, granular cell tumors are considered malignant when a morphologically benign granular cell tumor metastasizes to regional lymph nodes or to distant sites or causes death. Fanburg-Smith et al. further characterized malignant granular cell tumors histologically from their benign counterparts when their constituent cells met three out of six histopathologic criteria: necrosis, spindling, vesicular nuclei with large nucleoli, increased mitotic activity, high nuclear to cytoplasmic ratio and pleomorphism. Still it may be difficult to distinguish malignant from benign forms of GCTs through light microscopy; therefore even sparse mitoses, mild nuclear pleomorphism, and spindling of the neoplastic cells should be reported as atypical features that raise the possibility of aggressive behaviour. N Gupta et al reviewing the clinical and histological characteristics of a case series of ten malignant GCTs, concluded that the malignant forms could be classified into two categories: both clinically and histologically malignant, and clinically malignant but histologically benign. Histological evidence of apparent tumoral infiltration in the tissue surrounding the tumour is a regular finding in malignant lesions.

Granular cell tumors have an uncertain histogenesis. In recent years many immunohistochemical and ultrastructural studies suggest a Schwann cell origin. The tumor cells stain positively for S-100 protein, neuron-specific enolase, CD 68 and NK1-C3 in almost all cases. Positivity with stains for myelin-associated P0 and P2 proteins, myelin basic protein, and Leu-7 is less consistent. They are negative for epithelial markers like CK, AE1 and AE2. Although conventional GCTs usually show consistent NSE and S-100 positivity, atypical and non-consistent immunohistochemistry has been reported. In our case, the tumour showed cytoplasmic positivity for S-100, NSE and CD68 in palate and lumbar swellings.

Management of granular cell tumours depends on their nature. Benign granular cell tumours have excellent outcomes after wide local excision; malignant tumours have poor clinical outcomes and prognoses. Malignant GCTs can be differentiated from benign GCTs via thorough examination of the patient during clinical presentation and histological examination of the excised specimen using the Fanburg-Smith criteria. While the reported extent of surgical excision for GCTs is variable, wide local excision is recommended, irrespective of the benign or malignant nature of the tumour, so as to ensure negative margins. For benign and atypical tumours, wide local excision is curative. In our present study, all cases were benign. As there are no proper guidelines on the management of these tumours, we are of the opinion that it is best to carry out wide local resection rather than a marginal resection or observation. The role of adjuvant chemotherapy and radiotherapy is uncertain, but should be considered in patients with recurrent and malignant GCTs or metastatic disease. All patients should be followed up for recurrence and distant metastasis regardless of the initial nature of the disease.

Benign and malignant GCTs have similar histopathology, and there are no clear histological diagnostic criteria for benign and malignant tumors. The following are suggestive of malignant GCT: rapid tumor growth, > 5 cm in diameter and karyokinesis in > 2/10 high-power fields; tumor cells are spindle shaped, with vesicular nuclei and nucleoli; high ratio of nucleus to cytoplasm with cellular pleomorphism; and tumor tissue necrosis. One study found that > 50% p53-positive cells and > 10% Ki-67 positive cells were significantly correlated with malignancy.

CONCLUSION
Granular cell tumours are often misdiagnosed due to their nondescript clinical findings, varied anatomical location and pathological features. Morphologically, the neoplastic cells resemble macrophages further making the task difficult. A detail history, clinical examination and systematic cyto-histopathological work-up followed by confirmation by IHC is necessary to make an accurate diagnosis in most cases. Nevertheless, although rare, the association of GCTs with malignancy should be considered and dealt upon carefully as it affects the management and follow-up.

REFERENCES

Source of Support: Nil.
Conflict of Interest: None Declared.
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Cite this article as: Asaranti Kar, Goutami Das Nayak, Pranati Pradhan, Debahuti Mohapatra, Sandeep Mohanty, Shushruta Mohanty. Clinico-Pathological Analysis of Granular Cell Tumor: Study from a Tertiary Care Centre. Int J Med Res Prof. 2017; 3(3):42-46. DOI:10.21276/ijmrp.2017.3.3.010