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Granular Cell Tumour near the Angle of Mouth on Buccal Mucosa: Case Report and Review

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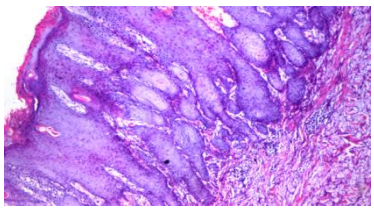
I. Introduction

Granular Cell Tumor (GCT) formerly known as Granular Cell Myoblastoma and Abrikosoff's tumor is a rare neoplasm. It is a benign lesion affecting the mucous membrane of the upper aerodigestive tract. GCT is a tumor of uncertain origin that has been variably considered a true neoplasm, a degenerative metabolic process or a trauma induced proliferation. Most GCTs are benign, but approximately 10% have malignant behaviour. Metastases to the regional lymph nodes and distant metastases have been observed. 1,2
We report a case of a GCT which presented as a nodular swelling of the buccal mucosa.

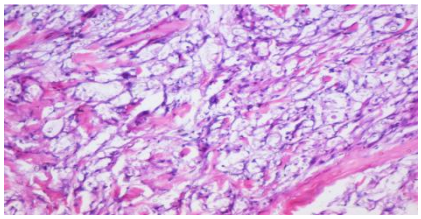
II. Case History

A 35 yr old male patient reported with a growth in the oral cavity. On examination, a well defined sessile growth measuring 2x1cms on the left buccal mucosa near the commissure was seen. The growth was whitish pink in color with an irregular surface . No lymph nodes were palpable. The lesion was provisionally diagnosed as fibroma clinically.

The lesion was excised and biopsy specimen measuring 2x.8cms, grayish white in color, with firm consistency was sent to the lab in 10% formalin. The tissue was grossed as required and processed.

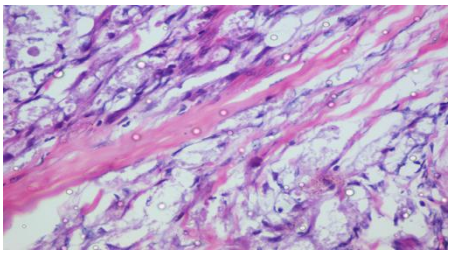


H&E under 4x magnification – Overlying epithelium showing pseudoepitheliomatous hyperplasia simulating squamous cell carcinoma Microscopic examination of H and E stained section showed over parakeratotic stratified squamous epithelium with pseudoepitheliomatous hyperplasia.



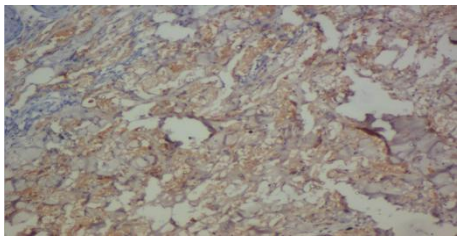
H&E under 10x magnification- Underlying connective tissue showing granular cells arranged in the form of ribbons separated by fibrous septa The underlying connective tissue showed numerous granular cells arranged in

sheets and ribbons, separated by fibrous septa. The cells were round to oval in shape, with distinct borders, and eccentrically placed nucleus. The cytoplasm showed numerous eosinophilic granules.

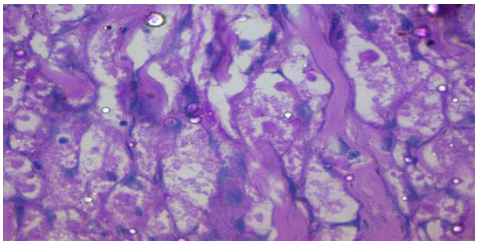


H&E under 40x magnification showing granular cells infiltrating into the muscle.

The granular cells appeared to be invading the muscle in few areas. Moderate inflammatory infiltrate predominantly composed of lymphocytes, few blood vessels lined by endothelial cells and extravasated RBC's were also seen. The granules showed a positive reaction to PAS stain and were immunohistochemically positive for S-100. Based on the findings, a histopathological diagnosis of Granular Cell Tumor was arrived at.
10x magnification- Granular cells showing positivity for S-100.



40X magnification - Granular cells showing positivity to PAS stain.



Cellularity/ pleomorphism/ mitosis

III. Discussion And Review Of Literature

GCT was first described by Weber in 1854, and established as a clinical entity by Abrikossoff in 1926 ,who termed it as Granular Cell Myoblastoma. It has been known by several names which include Abrikosoffs tumor, Myoblastoma, Granular cell neurofibroma and Granular cell schwanomma .(5)

Clinical Features

GCT is an uncommon benign lesion affecting the mucous membrane of the upper aero- digestive tract. Although GCT may appear in any site of the body 50% occur in the mouth, more precisely on the tongue. Cutaneous lesions constitute about 30% of cases, out of which only 1-3% are malignant. Typically, it appears as a single sessile and asymptomatic nodule rarely greater than 3cms. It is common in the 4th to 6th decade of life and has a predilection for females (1,2 10). Oral lesions present as a papule or nodule less than 3cms in diameter. They are asymptomatic, slow growing and generally covered by an intact mucous membrane of normal appearance, but can also be verrucous or pseudo-ulcerated. The tumor typically appears as a solitary lesion, although multifocal tumours at the first presentation have been reported in 4-10% of cases(2). Basili John R et al described a polypoid granular cell tumor of the oral cavity(9).About 25% of GCTs present as multiple lesions and Luana et al reported multiple granular cell tumors of the tongue and parotid gland.(12). About 10-20% of patients develop multiple lesions principally in the skin, soft tissues, breast and lungs. Sergio sarganti-Nito et al reported a multicentric granular cell tumour of ventral apical part of the tongue, lowerlip, groin. vulva, vagina and zygomatic process.(13)

Superficial lesions tend to protrude through the mucosa. But when more deeply located the tumor may simply be palpated as a firm mass. It is usually benign but sometimes it may be locally aggressive while 2% show metastases at a distant site. (5)

Pathogenesis

As with all lesions, the origin of GCT also has been a matter of debate since its description in 1926 by Alekeri Ivanovich Abrikosov a Russian pathologist (1875-1958). He classified GCT as having a myogenic origin and in 1970, Sequeria et al named it as Granular cell myoblastoma. Oliveria and Taube had doubts about the cell origin and preferred to consider it of mesenchymal origin. Reichler et al believed in a Schwann cell origin, as the tumour cell morphology was similar to its phagocytic form. (3) Many cell types have been implicated in its histogenesis, including muscle cells, Schwann cells, neuroendocrine cells, fibroblasts, neural sheath cells, undifferentiated mesenchymal cells and histiocytes. The histogenesis of GCTs has remained elusive despite a vast number of IHC and ultra structural studies. The diagnosis is mostly based on the histological findings and is confirmed by a positive IHC staining for S-100 and NSE. It also expresses Vimentin, PGP 9.5, NKI/C3 and CD68 while some markers such as Inhibin-α, Calretinin, Gelectin-3 and HBME show varying rates of staining.(3,4)

A large body of evidence at the morphological, ultra structural and immunohistochemical levels has been accumulating during the past years in support of the theory that the cells of origin for GCTs is neural with a schwannian differentiation. However, more recent findings have cast doubt on the neural origin of these tumors(6).

The IHC profile of GCTs has undergone extensive analysis. They are positive for S100 protein which serves as sound evidence for their schwannian /neural origin. CD68, a marker of lysosomes mostly associated with macrophages, is also usually positive in GCTs and its presence is explained by the assumption that Schwann cells acquire lysosomes during phagocytosis of myelin, a phenomenon which is known to occur in peripheral nerves showing Wallerian degeneration as well as in traumatic neuroma. (6).

The belief that GCTs are of Schwann cell origin has been questioned in light of the observation that myelin and myelin forming cells are extremely rare in the neurohypophysis and in spite of this, tumors with similar morphological grounds and ultra structural features of typical GCT are found at this site. (6).

Also, with the considerable progression and interpretation of immunohistochemical stains over the last two decades, together with the improvement of technical laboratory procedures, it became clearer that positive immunoreactions to S100 and CD68 cannot fully support a neural origin of the granular cells in GCTs. The variety of cell types positive for these proteins, is wider than was originally thought. S100 protein has been identified in cells of non neural lineages such as macrophages, normal skeletal muscle cells and rhabdomyoma and granular cells in Ameloblastoma. (6).

It is also noted the GCTs showed positive staining for p75, NKI/C3 and PGP9.5. These immunostains are not tissue specific but are rather expressed in a very large variety of adult tissues and their neoplastic counterparts. (6).

In addition, with a positive immunoreaction to inhibin α, the granular cells of GCTs take on, an immunoprofile, that may be better explained in terms of a stress induced degenerative process or a metabolic disorder, that leads to the evolvement of aberrant and uncharacteristic proteins and also loss of the cellular proteins and organelles that were once the foot prints of the cell of origin. (6).

Cytoplasmic granularity, such as that seen in GCT is not a unique feature of this lesion. It has been observed in various extents in cells in a vast array of conditions such as reactive `lesions, odontogenic cysts and tumors and other benign and malignant tumors. Granular cells have also been experimentally induced following exposure to cyclophosphamide. (6).

Also, lesions which exhibit granular cells have been found to be of neural, smooth muscle, striated muscle, endothelial, primitive mesenchymal, histiocytic and epithelial differentiation, further emphasizing the ambiguity of the granular cells. (6).

When granular cells of different cell lineages were ultra structurally analyzed they generally revealed lysosomal granules and cytoplasmic filaments, similar or identical to those observed in conventional GCTs. Collectively, these observations may indicate that on morphologic grounds, cytoplasmic granularity is not powerful enough to consider a GCT as being a distinct pathologic entity. Analogically, other cytoplasmic changes such as those recognized as clear, oncocytic, rhabdoid and signet cells which are not necessarily related to a specific cell of origin, are seen in many benign and malignant conditions and usually do not constitute a separate entity. (6).

Vered et al in their study noted the transition of striated muscle cells to granular cells as highlighted by Inhibin α staining results. This reflects the modification that striated muscle cells undergo and the process which gives them a granular morphology and an altered immunohistochemical phenotype that is completely unrelated to that of normal skeletal muscle. It was also found that similar modifications were seen in granular cells that

seemed to evolve from peripheral nerve fibers. This further strengthens the assumption that the appearance of granular cell is not limited to one cell type, but is rather site dependent and that the cell of origin may differ according to its accessibility at any site. However, the tongue is rich in nerve fibers encased by Schwann cells that could also be the source for GCTs that cannot be morphologically distinguished from those of muscle cell origin following an event of metabolic stress. In contrast, in the subcutaneous tissues, which are devoid of striated muscle fibers, other mesenchymal tissues, eg. Nerve fibers, smooth muscles and endothelial cells, could give rise to GCTs given that they undergo granular cell changes induced by metabolic stress. (6).

In summary, immunohistochemically, reactivity of the granular cells to a broad panel of antibodies such as S100, CD68, NKL/C3, PGP9.5 and inhibin α that characterize different tissues does not confirm any particular cell type for the histogenesis origin of GCTs. Furthermore, GCTs could be regarded as lesions that reflect a local metabolic or reactive change rather than a true neoplasm. 6

Microscopically, GCT consists of proliferation of large polygonal, oval or bipolar cells with abundant, fine or coarsely granular cytoplasm and a small, pale-staining or vesicular nucleus eccentrically located in the cell. The cell membrane is moderately distinct and some cells may contain large clumps of the granular cytoplasmic material, perhaps with clear halos surrounding the clumps. Granular cells often occur in ribbons separated by fibrous septa, giving the appearance of cells infiltrating or invading into underlying tissues, especially muscle, with the bipolar shape being more frequently noted at the leading edge. The cells may also appear to be streaming off from or metaplastically arising from underlying muscle fibres. Older lesions tend to become desmoplastic with a few scattered nests of granular cells in a densely fibrotic background. Granular cells demonstrating nuclear enlargement, hyperchromatism and pleomorphism or with mitotic activity or increased cellularity, are elements of the malignant variant of this tumour .The granular cells of oral and pharyngeal lesions typically extend to the surface epithelium, where they often induce a remarkable pseudoepitheliomatous hyperplasia and is often misdiagnosed as well differentiated Squamous Cell Carcinoma. Oral GCTs exhibit acanthosis and pseudo epitheliomatous hyperplasia in about 50% of the cases. It has been suggested that stimulation of basal cell proliferation occurs through an interaction between the granular cells and the neighbouring epithelial cells and this mimics Squamous Cell Carcinoma (9,14)

GCT must be included in the differential diagnosis of other granular cell lesions of the mouth that are benign or malignant such as granular cell leiomyosarcoma, non neural GCT, congenital epulis and Alveolar soft part sarcoma(10). Alveolar soft part sarcoma is merely composed of uniform sheets of large granular cells with few or no discernible vascular channels. The individual cells are large, rounded or more often polygonal and display little variation in size and shape. They have distinct cell borders and one or more vesicular nuclei with small vacuolated cytoplasm. At the margin of the tumour, there are usually numerous dilated veins, probably the result of multiple AV shunts in the neoplasm and PAS stain reveals varying amounts of intracellular glycogen and characteristically PAS-positive, diastase resistant rhomboid or rod- shaped crystals. The cytoplasmic granules of Granular cell leiomyosarcoma also are PAS positive and diastase resistant but these tumors are positive to Smooth Muscle Actin and Muscle-Specific Actin. (15) Granular cells of Congenital Granular Cell Epulis (CGCE) are more tightly and homogenously packed than those of GCT. The lesional margins of CGCE are more circumscribed than those of GCTs and there is no pattern of infiltration or invasion into the surrounding tissue, as is often seen in GCT. The overlying epithelium of CGCE demonstrates stratified squamous epithelium that lacks reteridges and that is sometimes slightly thinned as opposed to the epithelium of GCT that often shows epithelial hyperplasia or even pseudoepitheliomatous hyperplasia. A CGEC is more vascular than a GCT and exhibits a prominent complex network of vascular channels that are often dilated. (8)

Md.El.Khala.et al reported a case of ulcerative GCT, a rare variant, which is not fully studied in the literature and there are no previous descriptions for the clinical characteristics of this ulcer in addition to the histological and immunohistochemical features.The main challenge to ulcerative GCT is the resemblance to infectious granulomatous ulcers.(4) John R Basili et al reported a case of polypoid non neural granular cell tumor occurring in the oral cavity which lacked staining for S100 and NSE. (9)

Malignant GCT is extremely uncommon representing 2% of all GCTs.Malignant GCT occurs most frequently on extremities rather than the head and neck region including the oral cavity. Clinically, malignancy is suggested by rapid growth, large size, pain and invasion of adjacent structures. In malignant GCT, metastatic spread is a common finding. Fanburg-Smith et al proposed microscopic criteria to classify and predict the biologic behaviour and malignant potential of GCT which include necrosis, wide cellular sheets/ distribution of cells in fusiform strings, large nucleus with vesicular core, large nucleoli, increased mitotic activity (> 2 mitosis per 10 HPF), high N/C ratio, nuclear pleomorphism and spindling. GCTs presenting three or more of these criteria are classified as histologically malignant, those with one or two criteria are classified as atypical, and those presenting only nuclear pleomorphism, without any additional criteria are classified as benign. When malignant, the tumour can occasionally present local aggressiveness and in 2% of the cases, distant metastases

(regional lymph nodes, bones, peripheral nerves, peritoneal cavity and lungs.(3).(1,2) Clinical or histological evidence of malignant GCT requires the patient to be evaluated for the presence of occult metastatic disease(12).

A correct exicisional biopsy with adequate margins of safety and subsequent histopathological analysis is essential for correct diagnosis and treatment. An initial deep incisional biopsy is necessary to detect any pseudo-epitheliomatous hyperplasia which may lead to erroneous diagnosis of Squamous Cell Carcinoma. A low rate of recurrence of the lesion has been reported. Radiation and Chemotherapy are not recommended because of the tumor's resistance and potential carcinogenic effect. Strict follow up is mandatory in all cases to rule out and to evaluate for malignant transformation (5)

IV. Summary And Conclusion

GCT is a benign lesion most commonly occurring in the tongue. The granular cells demonstrate a wide array of cytological features in terms of cell shape and position of the nucleus. It also exhibits different architectural patterns, but they all still exhibit a benign behavior and do not recur irrespective of the status of the margins. Immunoreactivity of the granular cells to a broad panel of antibodies such as p75, S100, vimentin, NKI/C3. PGP9.5 and inhibin α characteristic of different tissues does not confirm any particular cell type for the histogenetic origin of GCTs. Furthermore GCTs could be regarded as lesions that reflect a local metabolic or reactive change rather than a true neoplasm.

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