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Oral Granular Cell Tumor: Histogenesis - An Immuno-Histochemical Profile

KEYWORDS: Granular cell tumor; Immunohistochemistry; Immunohistochemical (IHC) markers; Histopathogenesis

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ABSTRACT *A granular cell tumor (GCT) is an uncommon benign neoplasm affecting any part of the body, with a great percentage of lesions being reported to occur intraorally. One such case of GCT on the lateral margin of the tongue in a 17 year old girl is being reported.*

The histopathological diagnosis of GCT was confirmed by immunohistochemistry findings. The tumor was positive for S-100, NSE, Vimentin, CD-68 and negative for SMA and Desmin which helped us not only in arriving at the final diagnosis of GCT but also helped us to identify the origin of the tumor. Surgical resection of the tumor with wide margin was done and regular follow up of the patient for 2 years has not shown any evidence of recurrence and metastasis.

INTRODUCTION:

Granular cell tumor (GCT) was first described by Abrikossoff in 1926 as a tumor of myogenic origin. Hence, GCT was termed as myoblastoma, or as tumor of Abrikossoff.[1] Later it was thought to be of neurogenic origin and was also called as granular cell neurofibroma or granular cell schwannoma.[2]

Various authors have proposed different cells in the histogenesis of GCT. It is thought to arise from myoblasts, histiocytes, fibroblasts, undifferentiated mesenchymal cells and schwann cells.[2]

Although GCT is benign in nature, few cases have been reported with recurrence or metastasis to regional lymph nodes. The malignancy rate is estimated to be less than 2% of all reported GCTs.[3]

GCTs are reported to occur most frequently between 4th-6th decade of life and is rare below that age group.[1,2] An interesting case of intraoral GCT that is very rarely reported in adolescent population is being reported. It's clinical and histopathological findings are discussed. The IHC markers that helped us in the final diagnosis and evaluation of the cell of origin of this tumor is elaborated.

CASE REPORT

A 17-year-old girl presented with a painless swelling since 8 months in the left lateral margin of the tongue. On clinical examination, a single, firm nodular mass about 1cm in dimension was seen on the left lateral border of the tongue. The swelling appeared normal in color, without any secondary changes. There was no regression in the size of the swelling since the past 8months. It was not tender on palpation. Excisional biopsy was performed under local anaesthesia and specimen sent for histopathological analysis.

Fixation of the specimen was performed in 10% buffered formalin and embedded in the paraffin wax. 4-µ thickness of tissue sections were obtained from the paraffin-embedded block and stained with haematoxylin-eosin. Microscopically, the surface of the lesion was covered by stratified squamous epithelium, which exhibited pseudoepitheliomatous hyperplasia (Fig.1). Numerous foci of granular cells in the connective tissue, which were separated by fibrous septae was seen. The granular cells were large, polygonal to oval in shape with abundant pale, fine granular, eosinophilic cytoplasm and a small, vesicular, eccentrically placed nucleus. The cell membrane was distinct and well defined (Fig.2). The granular cells were seen invading the underlying muscle. There was no evidence of areas of necrosis. These findings were consistent with the diagnosis of granular cell tumor. The histopathological differential diagnosis of other granular cell tumors, such as granular cell leiomyoma, non-neural granular cell tumor, congenital epulis and alveolar soft part sarcoma were considered and hence an immunohistostaining for S-100, SMA, Neuron-specific enolase(NSE), Desmin, CD-68 and Vimentin was taken up for definitive diagnosis. The IHC staining showed positive immunoreactivity for S-100 (Fig.3), CD-68 (Fig.4), Vimentin (Fig.5) , NSE (Fig.6) and negative immunoreactivity for Desmin (Fig.7) and SMA (Fig.8), which helped us in arriving at a conclusive diagnosis of GCT. Post-operatively the patient showed good healing and a regular follow up for 2 years since the diagnosis and treatment has been uneventful without any evidence of recurrence and metastasis.

DISCUSSION:

GCT is a relatively uncommon benign neoplasm that occurs in almost any part of the body such as skin, nervous system, gastrointestinal tract, urinary bladder, female reproductive tract and bronchus.[2] The head and neck region is involved in about 45 to 65% of the patients with this tumor and 70% account for intra oral lesions.[2] The tongue, buccal mucosa, and hard palate are commonly affected.[3] However, tumors of the lip, gingiva, uvula and parotid gland have also been reported.[2]

The tumor most frequently occurs in the fourth to sixth decades of life and is rare in children. Females are twice commonly affected than males.[1,2] Cases of multiple lesions of GCT have also been reported.[6] Generally, it presents as a solitary asymptomatic nodule on the subcutaneous or submucosal tissues. It shows slow growth[1], usually not extending more than 3 cm in size. The mass appears pink in color but occasionally has a yellowish surface coloration and is firm in consistency. The overlying epithelium is usually intact. Sometimes the large lesions may show surface ulcerations, which

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may clinically give an impression of a malignant neoplasm.[2] Apart from the histopathological picture, the clinical size of the tumor, pain, rapidity of growth, invasion to underlying and adjacent structures and the presence of regional and distant metastasis will aid in differentiating a benign GCT from the malignant counterpart.[2]

In the present case, it was seen to occur in the unusual age of 17 year old girl patient with the site of occurrence and the clinical presentation being in accordance to the other reported cases of benign GCT.

Controversies regarding its histopathogenesis, behavior and variable localization still exists.[1] Vered et al. have advocated that the granular nature of the tumor cells in GCT reflects a local degenerative or metabolic or reactive change or lysosomic effect rather than a true neoplasm.[4] Nonetheless, some authors have proved a peripheral nerve-related cell as the cell of origin for the majority of these tumors and have supported it by the immunohistochemical investigations. [3] The neural origin has been widely accepted presently.[5]

Histopathologically, granular cell tumors exhibit round or polygonal cells with small eccentrically placed nuclei and abundant pale eosinophilic granular cytoplasm.[2,6] These cytoplasmic granules are assumed to be lysosomal structures. [7,6] The cells are usually arranged in cords and nests. The cell borders are generally distinct giving rise to a syncytial appearance. Sometimes the tumor appears to infiltrate the adjacent connective tissue. On occasions, there appears to be a transition from normal adjacent skeletal muscle fibers to granular tumor cells. This finding has suggested the muscle tissue origin for this tumor. Less frequently groups of granular cells may be seen enveloping small nerve bundles.[6] The overlying epithelium of the lesion shows pronounced pseudoepitheliomatous hyperplasia which could be misinterpreted as squamous cell carcinoma.[2] The malignant variant of GCT, shows the characteristic features of necrosis, polymorphic tumor cells, vesicular nuclei with large nucleoli, abundant mitoses etc.[1] Few cases show extensive hyalinization and calcification in between the granular cells, which suggests a long standing GCT with reactive changes.[4]

Based on our histopathological findings and correlating the clinical findings, we diagnosed it as a benign GCT.

The histopathological differential diagnosis for granular cell tumors is granular cell leiomyoma, non-neural granular cell tumor, congenital epulis and alveolar soft part sarcoma.[5]

Granular cell leiomyoma is an uncommon neoplasm in the oral cavity. It primarily occurs in the lips and is rarely seen in other areas such as tongue, cheek, palate and gingiva because of the scarcity of smooth muscles in these areas. It is seen in any age group, with a slight prevalence in men. Immunohistochemical reactions confirm the smooth muscle origin of the cells since they are positive to smooth muscle actin (SMA) and desmin, and are negative to S-100.[5](Table.I)

Another important differential diagnosis is the non neural granular cell tumor. It differs from GCT clinically as it has an expansive growth and histopathologically since it shows cellular atypia. Immunohistochemically, strong positivity for vimentin, weak positivity for CD-68 and smooth muscle actin (SMA), and negative staining for S-100 is noted in these lesions.[5](Table.I)

Congenital epulis should also be considered in differential diagnosis of GCT. These are rare tumors that can be located on the alveolar crest or in the tongue of newborn babies, with higher prevalence in females. Immunohistochemical study indicates negative to S-100, smooth muscle actin, CD-68 and desmin .[5](Table.I)

Alveolar soft part sarcoma (ASPS) is a malignant lesion, which can be confused with GCT due to its histological similarity. Most cases of ASPS are observed in teenagers and young adults, with a higher prevalence in females, and metastasis to the lung, brain and bones. Histologically, PAS positivity to intracytoplasmic rod-shaped crystals is seen in ASPS. In addition, immunohistochemical reactions show focal positivity to desmin and smooth muscle actin, and negative reaction to S-100.[5](Table.I)

Immunochemistry besides helping to establish the correct diagnosis helps in giving an insight to the origin of this tumor. Immunohistochemical studies of granular cell tumors suggest a neural or neuroectodermal origin of the granular cells.[2] The neurogenic origin is supported by positive immunohistochemical findings of neuron specific enolase and S-100 protein markers in these tumor cells.[2] (Table.I)

In order to eliminate the different tumors containing granular cells and arrive at a conclusive histopahological diagnosis we had to undertake IHC staining. Our findings of positivity to S-100, NSE, Vimentin and CD-68 and negativity for SMA and Desmin, helped us to conclusively diagnose it as a granular cell tumor of neurogenic origin.

A majority of these tumors follow a benign clinical course. Therefore, the treatment of choice is a conservative surgical excision of the lesion. [1,2] However as the GCT has poorly defined margins, it is suggested that the tumor should be excised along with normal adjacent tissue.[2]A low rate of recurrence of the lesion has been reported. Radiation and chemotherapy are not recommended because of the resistance of the tumor and potential carcinogenic effects .[3, 2] In 15% of cases, local relapse are possible due to incomplete excision of the tumor. Recurrence has also been reported in 1% to 3% of cases even with complete surgical excision of tumor with wide margin [2]. A strict follow up is mandatory in all cases to rule out recurrences and to evaluate for malignant transformation.[2, 1]

An excisional biopsy with wide margins has sufficed in the present case as there is no evidence of recurrence or metastasis in the two year follow-up of the patient.

CONCLUSION:

GCT is a benign tumor without much prognostic implication to the patient, when treated appropriately. However, it is important to arrive at a conclusive diagnosis of GCT, since there are a wide spectrum of tumors, having granular cells showing varying behavior, which alters the treatment planning and the prognosis of the patient. The definitive diagnosis can be established by IHC techniques.

Although surgical excision of the GCT with wide margins has been suggested as the treatment of choice, few cases have shown recurrence and metastasis to the regional lymph nodes. To some extent, this behavior of the GCT could be predicted by correlating the malignant nature of the tumor clinically and histopathologically. Only further reports of the GCT along with the regular follow up reports will help us in understanding and predicting the nature of this tumor.

IHC findings in different granular cell tumor

	S-100	SMA	DESMIN	CD-63	CD-68	NSE
Granular cell leiomyoma	Negative	Positive	Positive			
Non –neural GCT	Negative	Positive (weak)		Positive (strong)	Positive (weak)	
Congenital epulis	Negative	Negative	Negative		Negative	
Alveolar soft part sarcoma	Negative	Positive (focal)	Positive (focal)			
Granular cell tumor (GCT)	Positive	Negative	Negative	Negative	Negative	Positive

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Figure Legends

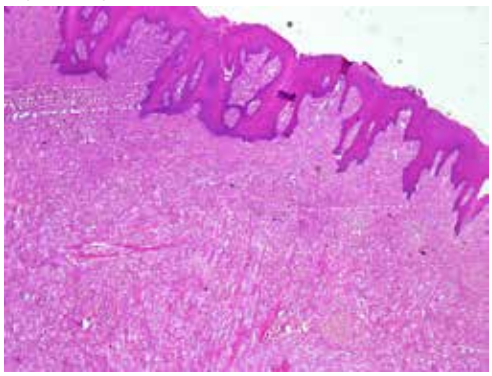

Fig 1: Photomicrograph of the granular cell tumor showing epithelium tissue and granular cells with fibrous septum in connective tissue (hematoxylin and eosin, magnification- 100x).

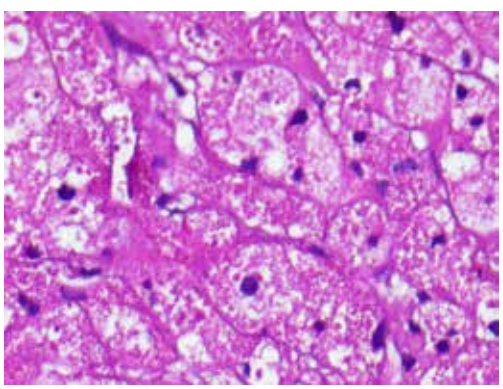

Fig 2: photomicrograph of granular cell tumor showing granular cells (hematoxylin and eosin, magnification-400x).

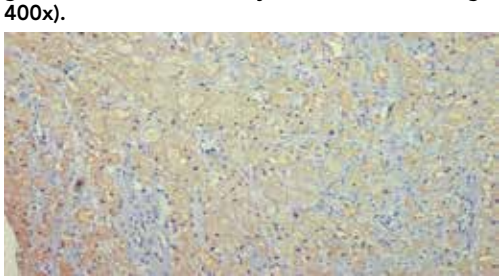

Fig 3: Photomicrograph of granular cell tumor showing positive immunoreactivity of S-100. (magnification -400x)

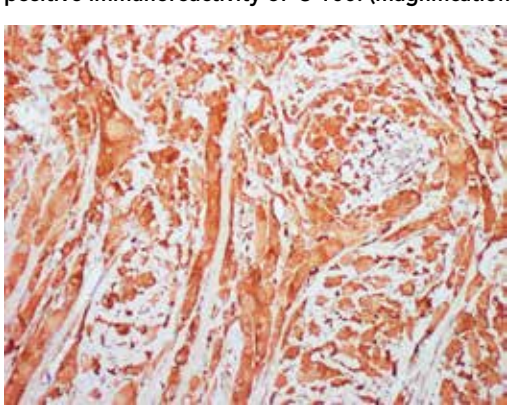

Fig 4: Photomicrograph of granular cell tumor showing positive immunoreactivity of CD-68 (magnification -400x)

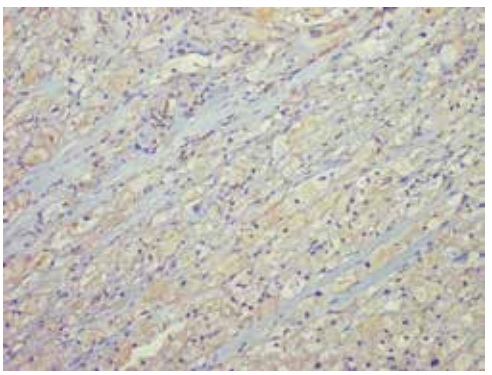

Fig 5: Photomicrograph of granular cell tumor showing positive immunoreactivity of Vimentin (magnification -400x)

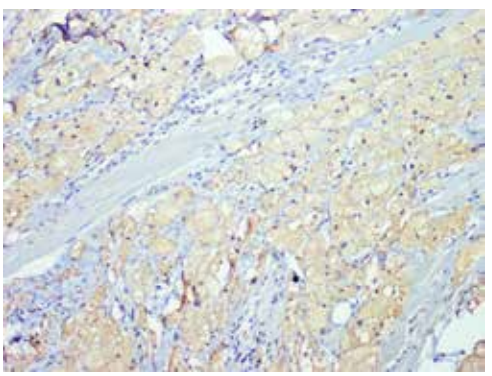

Fig 6: Photomicrograph of granular cell tumor showing positive immunoreactivity of NSE (magnification -400x)

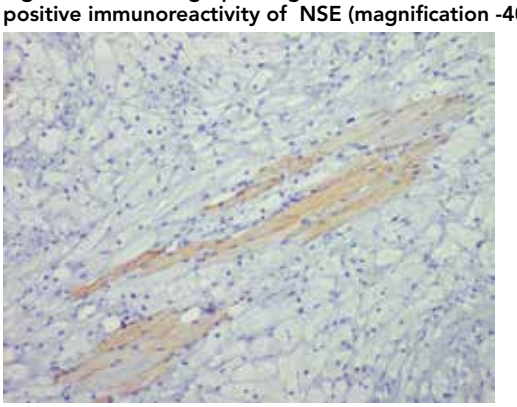

Fig 7: Photomicrograph of granular cell tumor showing negative immunoreactivity of Desmin (magnification -400x)

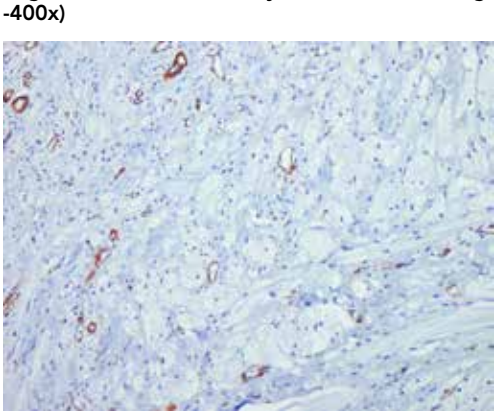

Fig 8: Photomicrograph of granular cell tumor showing negative immunoreactivity of SMA (magnification -400x)

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