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Pediatric Granular Cell Tumor of the Breast: An uncommon neoplasm in an uncommon site and age group

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ABSTRACT

Granular cell tumor (GCT) is a rare soft tissue neoplasm of Schwann cell origin. Most cases occur in adults; however, the precise incidence is unknown in children. GCT is usually a slow-growing, painless tumor involving the skin and soft tissues that is mostly located in the head and neck region, especially the tongue. The breast is one of the least common sites involved by GCT. This paper presents a 3-year-old girl who presented with a soft to firm, ill-defined swelling on the right breast with painful ulceration of the overlying skin. Fine needle aspiration rendered an initial diagnosis of fibrocystic change accompanied by apocrine metaplasia. Histologic evaluation of the excised breast mass revealed a benign granular cell tumor. Although rare, GCT of the breast should be included in the differential diagnosis for breast masses in pediatric patients. Proper diagnosis and timely management of this tumor are essential because of its malignant potential (<2% of cases) and high rate of local recurrence if not properly excised.

Keywords:
Breast; Schwann Cells; S100 Proteins.

INTRODUCTION

Granular Cell Tumor (GCT) is a rare soft tissue neoplasm of probable Schwann cell origin.[1,2] In 1926 this tumor was first described by Abrikossof who named it as granular cell myoblastoma thinking the tumor originated from myofibroblasts.[1,2] In 1962, Fisher and Wechles confirmed the neural origin of the tumor.[2] GCT most commonly affects adults between 30 and 60 years of age, and it has an exceptional occurrence among children.[3] GCT occurs most commonly in the head and neck, and 40% of all cases arise in the tongue.[4,5] The breast is involved exceptionally with an overall occurrence of 5-6% of all cases.[5] Taking into account of all GCTs in all the sites, females are affected 2-3 times more commonly than men.[3] Most lesions are painless and solitary. Notwithstanding 5-25% of the cases may be multiple.[2] Malignant cases account for 1-2% of all cases and show a poor prognosis.[2] Incidence is common in people of African descent.[4]

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CASE REPORT

A 3-year-old girl presented with ulcerated painful swelling over the right breast for one and a half months (Figure 1A). On examination, a soft to firm, ill-defined, ulcerated swelling measuring 3x2.2x1.5 cm at the upper outer quadrant of the right breast was noted. Doppler ultrasonography of the breast revealed a well circumscribed, hypoechoic mass with scant internal vascularity (Figure 1B).

Fine needle aspiration cytology (FNAC) was performed, and the smears revealed cellular clusters and singly lying cells with round centrally placed nuclei, bland chromatin, and abundant granular cytoplasm with indistinct cytoplasmic borders. The background showed occasionally scattered macrophages (Figure 2A and 2B).

The diagnosis of fibrocystic lesion of the breast with apocrine metaplasia was made. The skin nodule was excised. Grossly, the surgical specimen measured

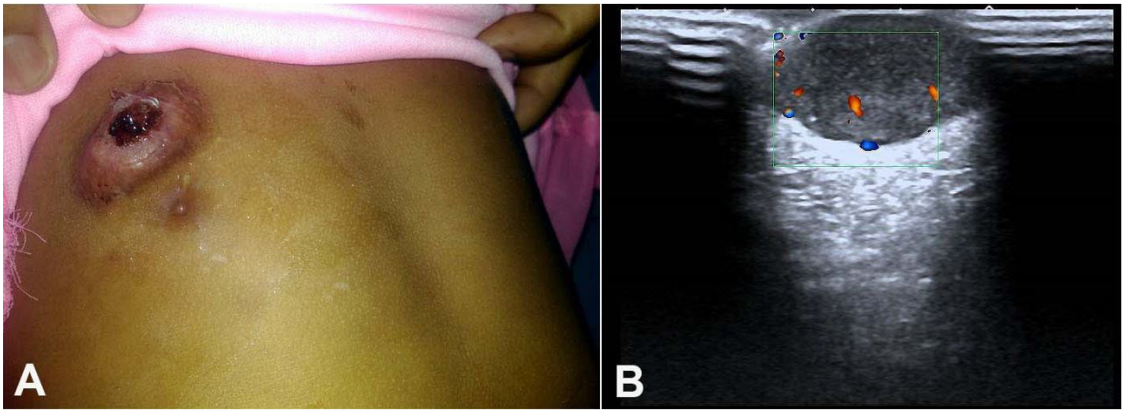

Figure 1. A – external examination of the right hemithorax showing the presence of an ulcerated swelling over right breast. **B –** Doppler ultrasonography of the breast revealing a well circumscribed hypoechoic mass with sparse internal vascularity.

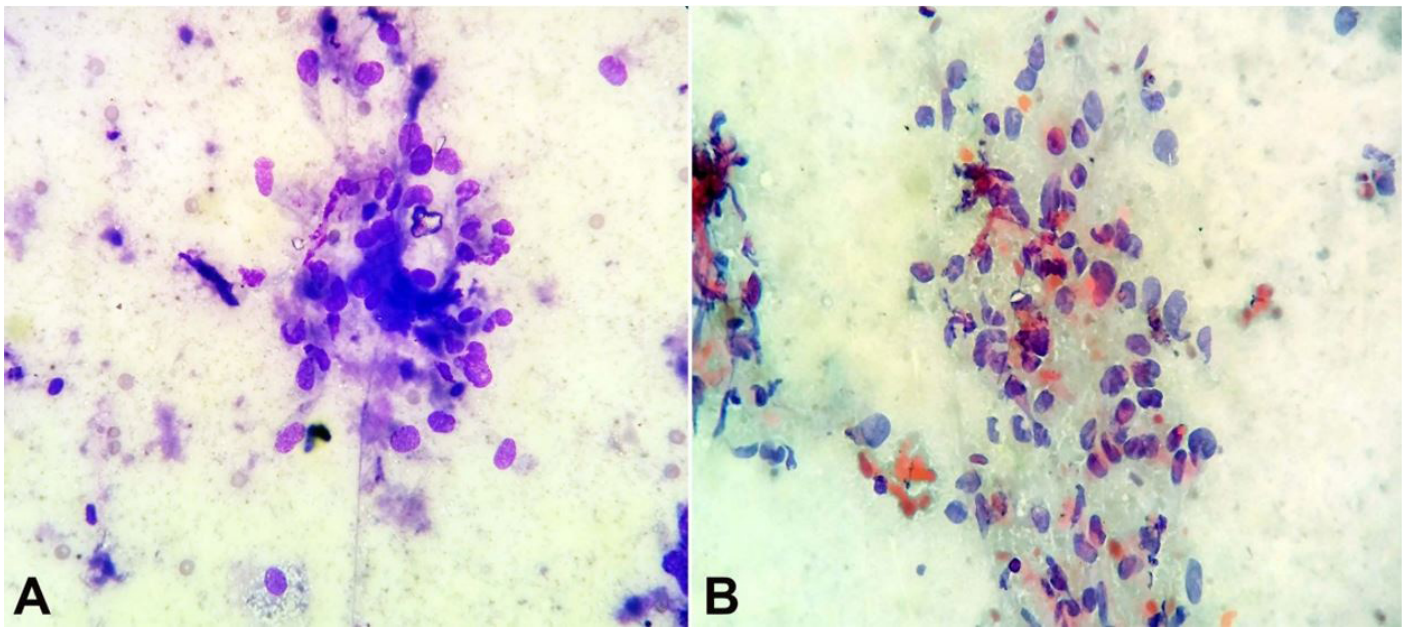

Figure 2. Photomicrographs of fine needle aspiration cytology showing clusters of cells with round, centrally placed nuclei, bland chromatin, and abundant granular cytoplasm with indistinct cytoplasmic borders (**A –** May-Grünwald Giemsa; **B –** Papanicolaou stain, 400x).

Figure 3. Surgical specimen showing a solid, light grey, well circumscribed nodule.

4.5x2.5x1.4 cm. The overlying skin showed a central ulceration and measured 1x1 cm (Figure 3), and the cut section showed a solid, light grey, well-circumscribed subcutaneous nodule involving the overlying skin measuring 3x2.2x1.5 cm.

The histopathological examination showed sheets of polygonal cells exhibiting abundant eosinophilic and granular cytoplasm and vesicular nuclei (Figure 4A). Mitoses were sparse with fewer than 1 per 10 high power field of 200x magnification. There was no necrosis. The tumor cells were Periodic Acid Schiff (PAS) positive and diastase resistant

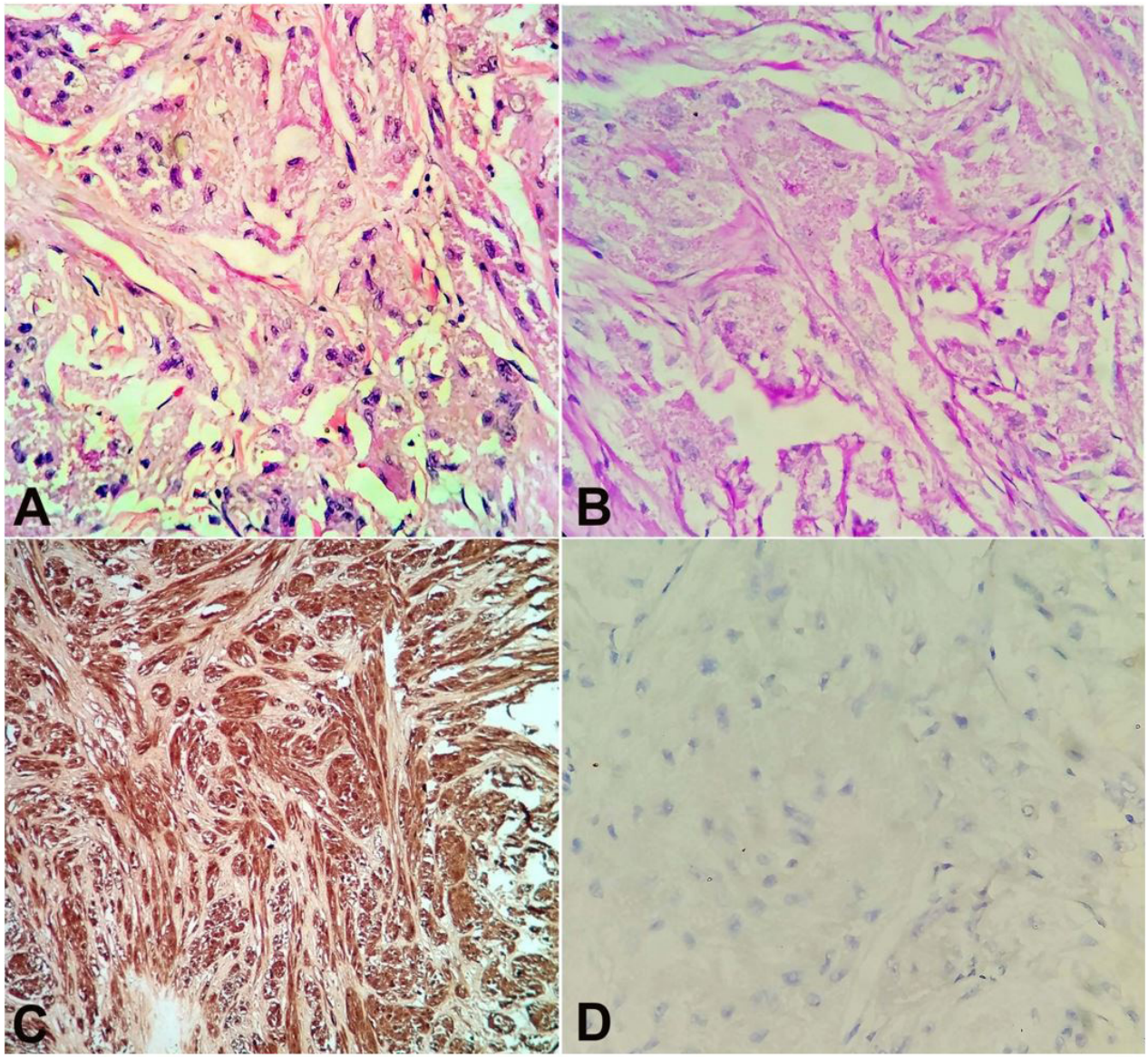

Figure 4. Photomicrographs of the tumor. **A –** sheets of polygonal cells exhibiting abundant eosinophilic, granular cytoplasm, and vesicular nuclei (H&E, 400X); **B –** The tumor cells were PAS positive and diastase resistant (PAS, 400X); **C –** The tumors cells were positive for S100 (200X); **D –** Ki67 index less than 1% (400x).

(Figure 4B). Immunohistochemistry showed S100 and neuron-specific enolase (NSE) positivity in the tumor cells. S100 showed both nuclear and cytoplasmic positivity in the tumor cells (Figure 4C). Ki67 index was less than 1% (Figure 4D) and p53 expression was negative. Thus, a final diagnosis of benign GCT of the right breast was made. All the surgical margins were free of tumor. After six months of follow-up, the patient is doing well without evidence of tumor recurrence.

DISCUSSION

Granular cell tumor is a rare soft tissue neoplasm of probable Schwann cell origin.[1,2] Clinically, cutaneous GCT has a nonspecific appearance rendering it a challenging diagnosis to make. GCT presents as an asymptomatic, solitary, hard nodule, occasionally sensitive and itchy, with variable coloration including native skin to brown-red color.[2] Most cases of GCT are benign but about 1-3% are malignant.[2]

Although GCT may occur anywhere in the body, the head and neck region is most frequently involved, accounting for 45-65% of all cases.[4] About 70% of the tumors in the head and neck occur in the oral cavity, most commonly involving the tongue.[4] Others sites include respiratory (10%) and gastrointestinal systems (4%-6%).[6] Breast is an uncommon location for GCT being involved in up to 6% of published cases.[4,5] GCT of the breast most commonly occurs in women in the fourth and fifth decades with a frequency approximately 1 in 1000 breast neoplasms.[5] It is extremely rare in children.[3]

To the best of our knowledge, only 7 cases of breast GCT in children have been reported in the English literature (Table1).[7-13] Our case is the youngest of the 7 reported cases. While most of the reported cases presented with a unilateral painless breast mass, our patient presented with a unilateral painful breast mass, with the pain likely attributed to ulceration of the skin, which is usually not seen in breast GCT (Table 1). The present case is rare due to its uncommon site, age at occurrence, and clinical presentation.

Cytologically, breast GCT has a varied differential diagnosis including benign lesions like fibrocystic lesion with apocrine metaplasia, fat necrosis, and malignant tumors like ductal carcinoma with apocrine metaplasia.[14] In the present case, the cytological diagnosis was a fibrocystic lesion of the breast with apocrine metaplasia as the cells showed abundant cytoplasm that was interpreted as apocrine metaplasia of the ductal epithelial cells.[14] Cytologically apocrine

Table 1. Cases of breast GCT in children reported in the English literature

Authors	Age (Y)	Gender	Clinical presentation	Tumor size (cm)	Side and location	Cytological diagnosis	Histological diagnosis
Apisarnthanarax[7]	15	F	Painless mass; No skin changes	1.5	Left breast	Not known	GCT (Excision)
Aderiran[8]	17	F	Mass	0.9	Left breast	Not known	GCT (Excision)
Yang [9]	17	F	Palpable painless mass	2.7	Right sub-areolar	Not done	GCT (core and excision)
De Simone[10]	14	F	Palpable intermittently painful mass; No skin retraction	2.6	Left upper inner quadrant	Not done	GCT (core and excision)
Marshall[11]	15	F	Two palpable painful masses; No skin changes	1.1	Both masses in right breast	Not done	GCT and fibroadenoma (Excision)
Heinzerling[12]	15	F	Palpable painless mass; No skin changes	3	Right upper outer quadrant	Not done	GCT (Excision)
Omar[13]	9.1	F	Palpable painful mass; No skin changes	1.1	Right upper outer quadrant	Not done	GCT (Excision)
Present case	3	F	Palpable mass; Skin ulceration	4.5	Right upper outer quadrant	Done	GCT (Excision)

cm = centimeter; F = female; GCT = granular cell tumor; Y = years.

cells have a well-defined cytoplasmic border in contrast to the undefined cytoplasmic borders characteristic of GCT cells.[14] Moreover, the cytoplasmic granularity is more prominent in GCT.[14] Benign breast lesions have two-dimensional sheets comprised of ductal and myoepithelial cells, in contrast to syncytial or three-dimensional clusters of cells in GCT.[14]

Ultrastructural analyses and immunohistochemical studies based on the S100 positivity demonstrate that GCT originates from the Schwann cells.[15] Histologically, the tumor consists of a well-demarcated dermal proliferation of round or polygonal cells with a centrally located nucleus and granular eosinophilic cytoplasm.[16] Ultrastructural studies elucidated that the granularity seen on light microscopy is due to the numerous lysosomes at the ultrastructural level.[17] Cytoplasm contains pustulo-ovoid bodies which are Periodic Acid Schiff (PAS) positive and diastase resistant.[14,16] Usually, epidermis overlying the tumor shows pseudoepitheliomatous hyperplasia which introduces squamous cell carcinoma into the potential histologic differential diagnosis of GCT in the skin.[16] Apart from S100 and NSE, GCT shows a varying degree of positivity for a wide panel of markers including Inhibin A, Calretinin, Vimentin, Protein gene product (PGP 9,5), Melanoma directed monoclonal antibody NKI/C3, and CD68.[16,17]

Six diagnostic criteria were described for malignant GCT,[17] which include (i) Necrosis, (ii) Spindle formation in the cells, (iii) A vesicular nucleus with a large nucleoli, (iv) Increased mitotic activity (>2 mitosis/ 10 high-power fields at 200x magnification), (v) High nuclear to cytoplasmic ratio, (vi) Nuclear pleomorphism.[17] The presence of 3 or more of these criteria supports a diagnosis of malignant GCT.[17] Our patient's GCT diagnosis was of benign nature as none of the above criteria were present.

The expression of p53 and a high Ki67 index are associated with an aggressive clinical course.[18] In benign tumors, the p53 is negative, and Ki67 is under 1%, while the malignant cases express p53 and Ki67 in 10% and 30% of cells, respectively. [18] According to the current literature, local recurrence is related to insufficient surgical excision.[19] The recurrence rate after wide local excision with negative and positive surgical margins is 2-8% and >20%, respectively.[20] Therefore, assessment and reporting of surgical margin is crucial to lessen recurrences.[20] In our case, the lack of expression of p53, the Ki67 index less than 1%, and the negative surgical margins contributed to the lack of tumor relapse to date.

CONCLUSION

Although rare, granular cell tumor of the breast should be included in the differential diagnosis in pediatric patients presenting with a breast mass. It should be remembered that the tumor may arise in different locations. Cytopathologists should be aware of the pitfalls in diagnosing GCT on FNAC. Proper diagnosis and timely management of this tumor are essential due to its malignant potential (<2% of cases) and its high local recurrence with suboptimal excision. Total excision with wide margins is vital for treatment success.

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