



Diagnosis of Granular Cell Tumor in Male Breast Utilizing Fine Needle Aspiration Cytology Preparation: Case Report and Brief Review of the Literature

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Abstract

Granular Cell Tumors (GCTs) are rare neoplasms of the soft tissues. They collectively comprise 0.5% of all soft tissue tumors and are generally benign. The breast is the site of GCT in about 5-15% of the cases. Of those, only 6.6% occur in males. The most commonly affected demographic is middle aged, pre-menopausal African-American women. This case, however, describes a 48-year-old male who presents with a Granular Cell Tumor of the Breast (GCTB). GCTB presents a significant diagnostic challenge, as it can clinically and radiologically mimic a breast carcinoma and has an incredibly wide range of presentation. GCT should be included in the differential diagnosis of presentation of breast mass. Appropriate diagnosis of this mostly benign neoplasm is essential to avoid unnecessary aggressive treatment.

Keywords: Granular cell tumor; Breast; Benign; Diagnosis; Fine needle aspiration; Biopsy

ABBREVIATION

GCT: Granular Cell Tumor, **GCTB:** Granular Cell Tumors of the Breast, **US:** Ultrasound, **IHC:** Immunohistochemistry, **MRI:** Magnetic Resonance Imaging, **PET:** Positron Emission Tomography; **FNA:** Fine-Needle Aspiration, **NSE:** Neuron-Specific Enolase, **CEA:** Carcinoembryonic Antigen; **PAS:** Periodic Acid-Schiff, **TAA:** Tumor-Associated Antigen

INTRODUCTION

Granular Cell Tumors (GCTs) are rare neoplasms of the soft tissues, most commonly affecting the tongue, head and neck. However, GCTs are not limited to these regions, as these tumors have been found in surface epithelium, subcutaneous tissue, respiratory tissue, gastrointestinal tissue, genital tissue, and notably, breast tissue [1,2]. GCTs were first described by Weber in the tongue in 1854, and subsequently by Abrikossoff in the breast in 1926 [3,4]. Consequently, GCTs that present in the breast are often referred to as Abrikossoff tumors. Abrikossoff originally described the lesions as granular cell myoblastomas, but, in 1962 Fisher & Wechles confirmed a neural origin of the tumor [1,5,6]. The current understanding of GCTs is that they arise from Schwann cells, derived from neural crest cells [2].

GCTs represent 0.5% of all soft tissue tumors and are generally benign, with <1% associated with malignancy which demonstrate a poorer prognosis [2,5,6,7,8]. GCTs present as multiple lesions in 5-15% of cases, and 5-15% of all GCTs are found in the breast [2,9]. Of the variant found in the breast, only 6.6% occur in men [2].

Granular Cell Tumors of the Breast (GCTB) are most commonly found in the upper-middle and upper-medial quadrant, likely corresponding to their perineural cell origin and the distribution of the cutaneous sensory supraclavicular nerve [2]. However, in recent years, there have also been rare findings of GCTB arising in the anterior axillary line in the accessory breast [7,9]. The majority of GCTB have been observed in premenopausal African-American women between the ages of 30-50 [1,5]. GCTB is uncommon in other populations and is exceptionally rare in the pediatric population, with only 7 cases reported in the English literature as of April 2019 [6].

GCTBs represent a particularly problematic subset of GCTs due to the diagnostic challenges they present. Clinically and radiologically, GCTB mimics primary breast cancer which can lead to misdiagnosis [5,8,10]. GCTBs often present as a painless, rounded, mobile nodules, which correspondingly leads to an initial diagnosis as a fibroblastic tumor or carcinoma [5].

There are no effective preventative measures for GCT. Early detection combined with wide complete resection of the mass remains the best treatment, yielding the most favorable outcome [9]. In the cases of men with GCTB, early detection practices may be less instituted, potentially causing delayed detection and treatment.

CASE REPORT

A 48-year-old man presented with a right breast peri-areolar mass, which he felt one month prior to current presentation. The mass was firm, slightly movable located at the medial aspect of the nipple with no change in skin, and no axillary lymphadenopathy.

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High-resolution sonography over the lesion showed a hetero-echoic lesion with posterior acoustic enhancement measuring 1.6 X 1.2 cm. Fine needle aspiration of the mass was performed and was adequate enough to prepare a cellblock for performing immunohistochemistry (IHC) studies. Cytomorphologic examination showed a cellular specimen displaying clusters and scattered, singly lying round-to-polygonal cells with histiocytoid appearance, and indistinct cytoplasm (**Figure 1A**). The cells showed abundant granular cytoplasm (**Figure B**). Cellblock material showed infiltrating clusters of tumor cells arranged in nests and sheets in collagenous stroma (**Figure 1C**). IHC studies were performed on the cellblock material and the tumor cells were positive for Vimentin, S100 (**Figure 2A**), and CD68 (**Figure 2B**). Tumor cells were negative for Cytokeratins (**Figure 2C**) and SMA. Ki-67 proliferation index was low with 3% nuclear staining. The cytomorphology, together with the IHC profile were consistent with the diagnosis of granular cell tumor. The mass was surgically excised and all surgical margins were free of the tumor.

Histomorphologic examination of the excised mass showed infiltrating mass composed of large round and polygonal cells with abundant coarse granular eosinophilic cytoplasm,

arranged in nests and sheets in collagenous stroma infiltrating breast tissue and surrounding fibrofatty tissue. The tumor cells showed large eosinophilic granular cytoplasm with minimal nuclear atypia, rare to no mitosis, and absence of necrosis. The histomorphologic examination was confirmatory to the prior FNA cytology diagnosis.

As a benign tumor completely excised, the patient received no post-operative treatment. Patient was followed up for seven years with no evidence of recurrence or metastasis, and then was lost to follow up.

DISCUSSION

GCTs represent 0.5% of all soft tissue tumors. 5-15% of GCTs are found in the breast and only 6.6% of those are found in men. Less than 1% of GCTs are malignant [2]. This study presents a case of GCTB in right breast of a 48-year-old male. GCTB alone is considered an uncommon finding and the presence of GCTB in a male breast is particularly significant.

Clinically, GCTBs present as unilateral, solitary, hard, and generally painless masses, although occasional can present with mild pain as seen in current case. GCTs can also present

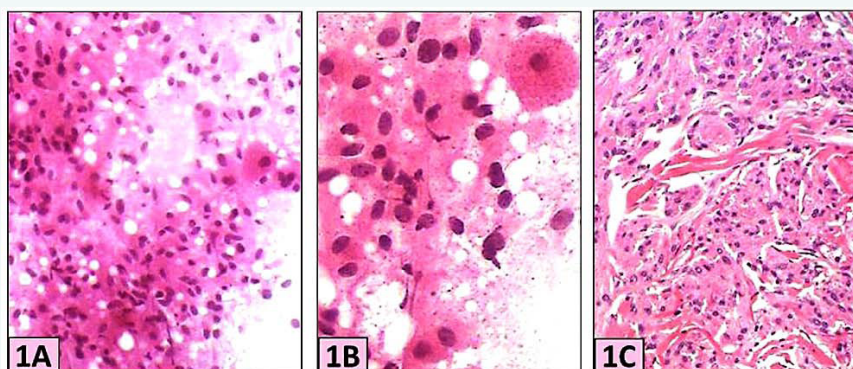


Figure 1 Breast mass, cytomorphologic features of FNA cytology preparation. **1A:** Cellular specimen displaying clusters and scattered, singly lying round-to-polygonal cells with histiocytoid appearance, and indistinct cytoplasm (H&E stain X40), **1B:** Tumor cells showing abundant granular cytoplasm (H&E stain X100), **1C:** Cellblock showing infiltrating sheets and clusters of tumor cells arranged in nests and sheets in collagenous stroma (H&E stain X40).

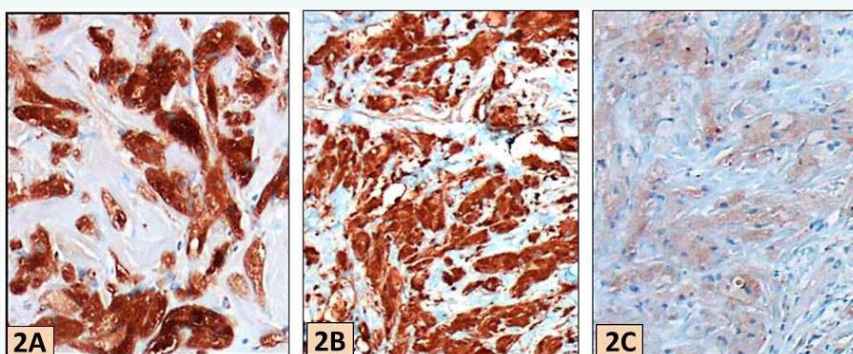


Figure 2 Immunohistochemistry studies on FNA cellblock cytology preparation. **2A:** Tumor cells positive for S-100, **2B:** Tumor cells positive for CD68, **2C:** Tumor cells negative for Cytokeratin AE1-3.



with nipple inversion, skin retraction and an infiltrative growth pattern with local invasion of the greater pectoralis muscle, mimicking malignancy [2,11,12]. This clinical feature-set is consistent for both men and women and poses a unique challenge in the diagnosis of GCTBs, often leading to a misdiagnosis of carcinoma or other aggressive malignancies, which share the aforementioned clinical features [5,11,12]. GCTs are usually benign but have a tendency to recur [13]. GCTs have a recurrence rate of 2-8% with clear resection margins, and 20% when the resection margins are positive for tumor infiltration [14].

Radiologically, GCTB can mimic breast cancer due to a wide range of presentation from a round well-circumscribed mass to an indistinct or speculated lesion on mammography. Microcalcifications are uncommon in GCTB which can assist in differentiating it from breast cancer. On ultrasound (US), GCTBs can present as solid, poorly marginated lesions with marked posterior shadowing, or as more benign-appearing well-circumscribed solid masses [7]. Notably, US also yields a unique anisotropic effect caused by the common internal fibrillary composition of the GCTB resulting in variable echogenicity depending on the angle of the US beam [2]. In Magnetic Resonance Imaging (MRI), GCTB shows lesions with low-intermediate signals in T1-weighted sequences, but hardly visible in T2-weighted sequences [2]. When using gadolinium contrast, GCTB appears as variably enhancing lesions with both benign and malignant features [2]. Mammography, US, and Magnetic Resonance Imaging (MRI) are all unable to identify any specific diagnostic characteristic due to this high degree of variability [2]. Interestingly, Positron Emission Tomography (PET) can differentiate GCTB from a malignant lesion, as, unlike malignant lesions, GCTB does not show an increase in metabolic activity [2]. A benign GCTB shows a PET uptake value of about 1.8, which is less than the cutoff value of 2.5 to signify malignancy [8].

Preoperative biopsy is essential in GCTB, but there is disagreement in the most optimal method of obtaining a tissue sample. Literature exists which supports that obtaining a tissue sample via Fine Needle Aspiration (FNA) is up to 93% effective (when combined with guiding US), however, some investigators point out to the shortcomings of FNA. They argue that the solidity of the mass may prevent proper sampling, and disruption to cellular architecture as well as insufficient material for immunohistochemical staining can increase the likelihood of misdiagnosis [2,7,15,16]. Some reports indicated that the quality of the smear may make interpretation more difficult, as cytoplasmic features may be interpreted as apocrine/histiocytic lesions, or membrane rupture may result in a dirty background [17]. Alternatively, biopsy with an 11-18 gauge core needle has been shown in a case cohort study of breast GCTB by Brown et al. to be effective and yield correct GCTB diagnoses in the 91 cases they reviewed [17].

Our case is in support of the efficacy of FNA in making full diagnosis of GCTB including confirmatory IHC studies without the need of tissue biopsy. The recent close integration of cytology and radiology has allowed for minimally invasive, safe, accurate, and cost-effective diagnosis of suspicious masses; which was previously accessible only by surgical biopsy techniques. As

a result, cytologists are increasingly called upon to diagnose disease in specimens procured under image guidance for different organs. Rather than causing delay, cytology facilitates timely diagnosis and management and is an integral part of a multimodal approach to various tumor diagnoses. On-site cytology interpretation increases the diagnostic yield of the procedure by allowing for additional needle passes as necessary [24].

Histologically, GCTB is composed of loosely infiltrating large round or polygonal cells with abundant coarse granular eosinophilic cytoplasm, arranged in nests and sheets in collagenous stroma. Nuclei are centrally located and can range from small and dark to large with vesicular chromatin [12]. Cells characteristically stain positive for S-100 Protein, CD68 (KP-1), neuron-specific enolase (NSE), Carcinoembryonic Antigen (CEA) and Periodic Acid-Schiff (PAS) [8]. Interestingly, there is a small subset of GCTs, known as non-neural type that stain negative for S-100 [18,19]. Consequently, histopathologists should exercise caution when typing these neoplasms. Finally, there is lack of consensus regarding the benefit of Calretinin in histological staining, but it may be useful in differentiation in conjunction with the other aforementioned markers [5].

GCTB uses widely accepted histopathological criteria for malignancy classification, as per the Fanbourg-Smith Criteria, of which 3 out of 6 must be met for the lesion to be classified as malignant. This includes: Spindling cells, increased nuclear/cytoplasmic ratio, vesicular nuclei with large nucleoli, pleomorphic nuclei, necrosis, and increased mitotic activity [20]. Additionally, malignant GCTs should be suspected when pathologically enlarged proximal lymph nodes are observed, the tumor is >5cm, there is infiltration of the adjacent tissues, or there is heterogeneous signal intensity or rim enhancement on MRI [21].

There are no effective preventative measures for GCT and early detection combined with wide complete resection of the mass has been considered the best treatment, yielding the most favorable outcome [9]. The gold standard of excisional biopsy remains the best definitive method for diagnosis, with a wide local excision recurrence rate of only 2-8% [2,7,15,16]. Clean margins are imperative as it has been noted that GCTs have a tendency for local recurrence [13]. Our presented case showed no evidence of recurrence with seven years follow up.

While novel treatment options have been sparse up until recently, minimally invasive ablative techniques are proving to be practical alternatives for treatment of GCTs. Cryoablation therapy, in particular, demonstrates a shorter recovery time due to the inherent analgesic properties of ice, and increases the cost-effectiveness of the procedure by utilizing fewer probes during the procedure. Cryoablation also leads to the activation of dendritic cells and secretion of pro-inflammatory cytokines like IL-1 α and TNF α , which may result in an upregulation of immune response, aiding the treatment and recovery. The treatment seems to maintain the structural integrity of tumor-associated antigen (TAA) molecules, while irreversibly damaging tumor cell membranes, causing an ideal ratio of coagulative necrosis/apoptosis [22].



This case and literature review aims to shed light on a significant diagnostic challenge. GCTB is often misdiagnosed due to its resemblance to breast carcinoma, potentially leading to over-treatment [2]. Early detection combined with wide surgical resection is the preferred management of GCTB and demonstrates a low recurrence. However, breast screening is not routine in men. This delay in early detection poses an additional diagnostic hurdle on top of the already dichotomous clinical and radiological presentation of GCTB. The definitive diagnosis is made through histopathological and immunohistochemical findings, which may aid pathologists in correctly identifying this neoplasm. Finally, it is important to note the usefulness of US with its particular sensitivity to the common internal fibrillary composition of the GCTB, and PET scans to discern GCTs from malignancies. Cryoablation is a treatment option to watch, as it may be a suitable and less invasive alternative to the presently accepted standards.

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