Breast granular cell tumor: A report of two cases and review of literature

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Key clinical message:

Granular cell tumor (GCT) is a rare breast neoplasm. There are only a few reports of breast granular cell tumors in the literature. Here in, we present two cases of female patients diagnosed with this tumor and perform a review of literature on the prevalence, diagnosis, histology, treatment, and prognosis.

Introduction:

GCT was first described by Abrikossof in 1926 [1]. They arise from Schwann cells and can be found in subcutaneous, intradermal, or submucosal tissues [2]. They can occur in any body site and may be multifocal [2,3] with head and neck, chest wall and arms being the most common sites [2,4]. GCT of the breast (GCTB) arises in the intralobular breast stroma and occurs in the distribution of cutaneous branches of the supraclavicular nerve [2]. GCTs are rare and GCTBs are even rarer. GCTB accounts for between 5 and 15% of all GCTs being mostly benign [5].

Case 1:

Patient is 63 years old female is seen for diagnostic evaluation of a breast mass detected on a PET-CT. Patient has a current diagnosis of a poorly differentiated neuroendocrine carcinoma of rectal origin, treating with chemotherapy and PET-CT detected a minimally avid left breast mass (Figure 1). The patient had

no personal history of breast or ovarian cancer, but she had a family history of breast cancer in paternal grandmother. Patient has also had a skin excision in right upper back in 2020 which was a granular cell tumor. Mammography revealed scattered areas of fibro glandular tissue (Figure 2) with no correlating finding. High-resolution real-time ultrasound of the left breast then showed an irregular mass with indistinct margins and echogenic halo measuring 11 mm in the left breast at 12 o'clock. This mass was biopsied under sonographic guidance yielding a benign granular cell tumor (Figure 3). A left axillary lymph node with a borderline thickened cortex was also detected, being biopsied yielding normal lymphoid tissue (Figure 4). A follow up PET-CT was performed, demonstrating a stable mass with low uptake and with a post biopsy clip (Figure 5).

Case 2:

50-year-old patient presents with a palpable mass in her right breast. Mammographic MLO view (Figure 6) demonstrates a sub centimetric irregular and spiculated mass in the upper outer quadrant of the right breast (arrow). Ultrasound (Figure 7) was performed and demonstrates a vertically oriented irregular mass with indistinct margins and hypoechoic echogenicity and marked posterior acoustic shadowing (arrow). A metallic marked was placed at the sonographic finding and the lateral mammographic view (Figure 8) demonstrates the correlation of the mammographic and sonographic findings. Ultrasound guided vacuum assisted biopsy was performed yielding a granular cell tumor of the breast. Post biopsy mammogram (Figure 9) demonstrates the hematoma and the post biopsy clip in the correct position (arrow).

Discussion:

Epidemiology:

GCTs are rare. According to a study at a single institution over 32 years, the overall incidence of granular cell tumors in surgical specimens was 0.03% [6]. Some other studies suggest a prevalence of 1:617 among the screened population and 6.7:1000 cases in the total clinical population [2,7]. GCTB can occur in both sexes, but is most common in women, with a female: male proportion ratio ranging from 1.8 to 2.4 [8,9]. GCTB can occur in all age groups but is more common in women in their 40s to 60s [6,10,11], although there have been cases identified in patients as young as 14 years old [12,13]. It is also more prevalent in African origin women, comprising about 60 to 70% of the cases [11,14,15].

Clinical presentation:

About 70% of cases of the GCTB are detected by palpation, 26% through screening and 4% during follow-up post breast malignancy [12,14,16]. Most of the palpable masses were painless, mobile, firm and elastic with some possible associated skins changes like thickening, tethering, dimpling and retraction. Some patients have reported pain or pruritus. Axillary lymph adenopathy is not common, most of the time being reactive [11,12,14]. GCTBs are usually solitary, but multiple lesions can occur within the breast or in combination with an extramammary mass in 18% of the cases [16]. In 10% of the cases there can be a concomitant malignancy, mostly ductal carcinoma [17,18]. Multiple GCTs should raise clinical concerns about associated syndromes such as Noonan syndrome, neurofibromatosis type I, and LEOPARD syndrome [19-24]. Some authors have reported PTPN11 gene mutations in granular cell tumors associated with LEOPARD and Noonan syndromes [22]. In another study, granular cell tumor was also associated with germline PTEN mutations in patients with PTEN hamartoma tumor syndrome [25].

Subtypes:

Traumatic granular cell neuromas can occur in mastectomy beds, close to surgical scars and mimic a recurrence. They show both characteristics of a GCT and traumatic neuroma, being indistinguishable in terms of histology and immunohistochemistry [19].

Malignant GCT.

Although GCTBs are usually benign, malignant GCTBs can be seen accounting for 1% - 2% of cases [19,26,27]. They differ clinically from the usual GCT, showing masses that grow fast with signs of local

invasion and associated axillary adenopathy. They show higher rates of local recurrence [4,28,29]. The breast can also be secondarily involved with metastasis from primary malignant GCT elsewhere. Recurrence and metastasis, however, can occur with histologically benign or atypical GCTs [14,30]. When metastasis occurs, the most common sites are lungs and bones and less commonly liver, bowel, breast, thyroid, heart, pancreas, spleen, retroperitoneum, pharynx, mouth, neck, and brain [3]. There is no staging system for malignant GCTB [31].

Histology:

On macroscopy GCTBs are firm, solitary masses, some of them circumscribed, with a capsule, but they frequently show an infiltrative growth pattern with non-circumscribed margins [14]. They are typically homogenous with a color ranging from white to tan [14]. They can be associated with fibrosis in 40% of cases [43]. When non-encapsulated, they may infiltrate into the surrounding tissues like fibrous tissue, adipose tissue and pectoralis major muscle [14]. Due to this growth pattern, GCTBs may resemble invasive breast carcinomas [12,16]. On microscopy GCTBs show an infiltrative growth pattern in nests, cords, or sheets of large polygonal and occasionally spindled cells with abundant eosinophilic, finely granular cytoplasm and small nuclei surrounded by sclerotic stroma [14,32]. GCTs have Pustulo-ovoid bodies of Milian, which are large granules with clear halos [14,32]. The granules are strongly period acid-Schiff (PAS) positive, and they represent lysosomes. Nuclei have dense chromatin, are relatively small, and are centrally placed [1].

Immunohistochemistry:

Both benign and malignant GCTs typically stain positively for S-100, a neuromelanocytic marker and for CD68 a marker of lysosomal activity. GCTs also stain positive for neuron-specific enolase, CD57, inhibin, calretinin, TFE3, SOX10, CD56, PGP9.5, and vimentin [11,14,33-36]. S-100 is strongly positive for GCT but is not specific since it can be seen in melanoma, micro glandular adenosis, and typically negative in breast carcinomas [11]. Some GCT have been described in pregnancy [37] and the immunohistochemical profile shows no hormonal dependence. GCTs lack estrogen or progesterone receptor and cytokeratin expression [14]. Microscopically, GCTB can resemble apocrine carcinoma, but GCTB lacks androgen receptors and apocrine carcinoma lacks S100 expression. AE1/3 epithelial markers can also help distinguish GCTB from invasive carcinoma because they stain negative in GCTB [14].

Malignant GCTB:

Histologic characteristics that are indicative of malignant GCTB are prominent nucleoli, a tumor diameter greater than 5 cm, elevated mitotic activity, necrosis and nuclear and cellular pleomorphism [28,29]. High Ki-67 proliferation index may also suggest malignant GCT [14,38,39], but Ki-67 >10% was seen in only 56% of malignant GCT in the series [39].

Imaging findings:

There are no specific imaging characteristics for GCTB, and they can mimic breast carcinoma [28,40].

Mammography:

They are present as irregular masses in 75% of the cases, circumscribed oval or round masses in 18% of the cases and with indistinct margins or architectural distortion in 8% of the cases [14,41]. They are often hyperdense or isodense [14]. Even if the mass is circumscribed, it is infiltrated on microscopy. Retrospective careful review of the images often demonstrates some focally indistinct or spiculated margins. Generally, microcalcifications are not seen [14,41,42,43]. GCTBs are usually small, less than 3 cm in diameter. Some other reported features are hypodense rim and heterogeneity [11,14,41]. GCTBs are frequently reported in the upper and upper inner quadrant of the breast in up to 83 % of the cases [40], which matches the cutaneous sensory branches of the supraclavicular nerve [7,40,44], but they are reported in all quadrants and in the axilla. GCTB can not only invade adjacent structures such as overlying skin or muscles [14], but also can invade adjacent fibroadenomas or lymph nodes [46] and be associated with fat necrosis [16] or breast malignancy [28,40].

Ultrasound:

Sonographic findings are not specific. The sonographic appearance depends on the degree of the tumor infiltration and reactive fibrosis. The most common features are solid masses with ill-defined margins, either hypo or hyperechoic, taller than wide with marked posterior shadowing and hyper vascularized. [11,12,14,28,41]. Marked hypoechoic masses have been reported in 56% of the cases, posterior acoustic shadowing in 48%, and mixed heterogeneous echotexture with areas of hyperechogenic or entirely hyperechoic in 44% of the cases [12,14,41]. Rarely they can be well circumscribed with posterior acoustic enhancement, being reported in 36% of the cases [41].

Magnetic resonance imaging:

There are not many reports on MRI findings of a GCTB. Most of them report oval or irregular masses with irregular margins, intermediate signal intensity in T1-weighted images and mild hyperintensity in T2-weighted images, with no surrounding edema [14,41,45]. After contrast injection, most GCTB are described having a homogeneous enhancement, but rim enhancement was also reported. Kinetics is variable. There are reports of slow and rapid enhancement [12,14,16].

PET

On PET-CT, GCTBs do not show any significant increased metabolic activity regarding glucose metabolism. The reported standardized uptake values were 1.7 to 1.8 [12,47].

Diagnosis:

Core biopsy is often sufficient to reach the pathological diagnosis [48,49]. Cells of a GCTB demonstrate intense positive S-100 staining, and notably stain negative for both progesterone and estrogen [12,28,40]. But sometimes it can be difficult to distinguish malignant from benign GCT on core biopsy and some non-representative biopsies can occur. For instance, when only the skin is sampled in a superficially located GCT this can show pseudoepitheliomatous hyperplasia, which can look like a squamous cell carcinoma. This pseudoepitheliomatous hyperplasia is reactive and found in over half of the GCTs [11]. Benign tumors can also demonstrate both vascular and perineural invasion, but these histologic features do not confer malignancy or an adverse prognosis [50]. Eventually GCT requires complete excisional biopsy since they can have patchy areas of malignancies and a core needle biopsy may not be representative of the entire tumor.

Differential diagnosis:

The most apparent differential diagnosis is scirrhous carcinoma. Some other differentials are granulomatous mastitis, fat necrosis, duct ectasia, myoblastoma, epithelial cells with apocrine features, dermoid cyst, desmoid tumor, duct ectasia, sclerosing adenosis, fibroadenoma, hidradenoma, hypertrophic scar, traumatic neuroma, keloid, lipoma, invasive mammary carcinoma, secretory malignancies, alveolar variant of ductal malignancy, histiocytic malignancy, apocrine carcinoma, basal cell carcinoma, fibrosarcoma, malignant fibrous histiocytoma, neurofibroma and schwannoma [11]. Although extensive, correct diagnosis can be achieved combining a careful histologic, immunohistochemical, imaging and clinical evaluation.

Treatment:

Surgery:

Excision of a GCTB is the standard treatment whether benign or malignant and it is often curative. Due to the infiltrative growth pattern of this tumor, wide surgical margins are needed and have been shown to diminish the recurrence risk [11,51]. Local excision of lymph nodes or sentinel lymph node biopsy is not indicated except in the cases of malignant GCTB [11,12,52].

Chemotherapy and Radiation Therapy

There is no current standard chemotherapy regimen or adjuvant radiation therapy for malignant or metastatic GCTs given the lack of randomized clinical trials with this specific lesion [11,53,54]. In the United States,

only 11.3% of patients with malignant granular cell tumors received radiation therapy [31].

Prognosis:

Benign GCTs show excellent prognosis even when recurrence is present [11,55]. With excision using wide margins, recurrence has been reported in 2-8% of cases [55]. When incompletely excised, the recurrence rates increase to 21% to 50% [29]. After removal of a GCT, some authors suggest that a long term follow up of 10 years should be performed because distant recurrences have been documented [56], but there is no clear consensus or standards on this matter [14]. Malignant GCTs have a worse prognosis, with 74% and 65% survival rates at 5 years and 10 years, respectively. Malignant GCTs show a recurrence rate of 32% to 41% and metastasis rate of 11 to 62% between 3 to 37 months after diagnosis [11]. Those with distant metastases at diagnosis have 0% survival at 5 years compared to 81% in those without metastases [11].

Conclusion:

Complete excision with negative margins and close clinical follow-up is currently the gold standard treatment strategy for both malignant and benign GCTB. More studies and clinical trials are still needed for deeper knowledge of malignant GCT and subsequent development of an effective treatment.

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Written informed consent for publication of the case report was taken from the patients

Authors contributions:

Assim Saad Eddin, MD: Drafting the manuscript

Umar Ramzan Bsc: Drafting the manuscript

Su Kim Hsieh, MD, PhD: Figure legends and image extraction, Revising the manuscript

Fabiana Policeni, MD: Revising the manuscript

Conflict of Interest Statement:

The authors hereby agree that there are no conflicts of interest to disclose.

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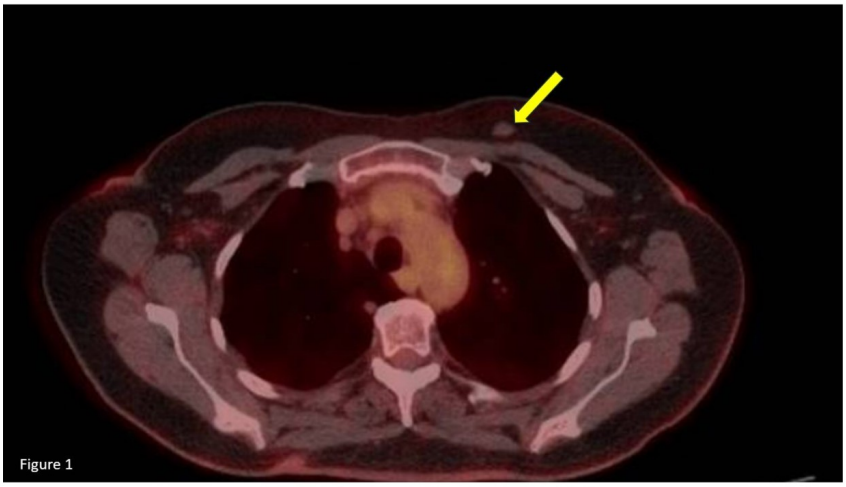

Figure 1

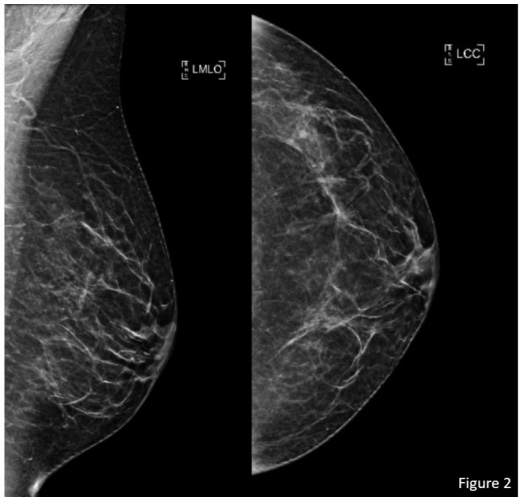

Figure 2

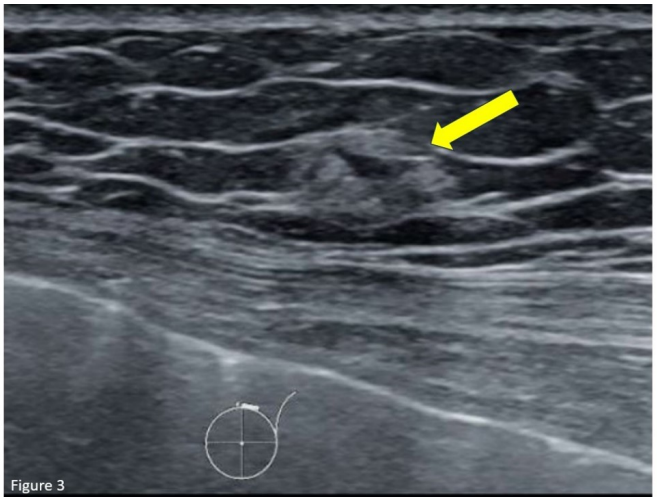

Figure 3

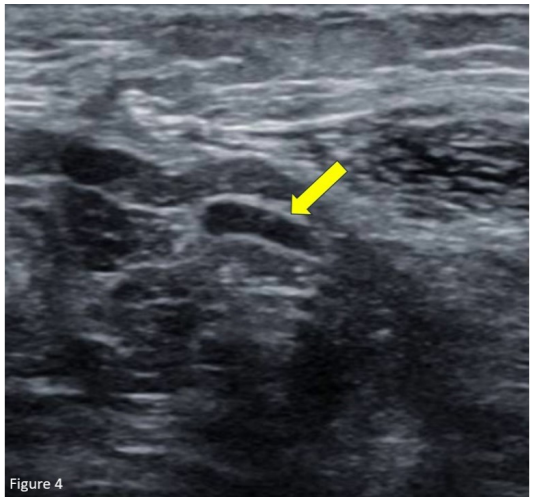

Figure 4

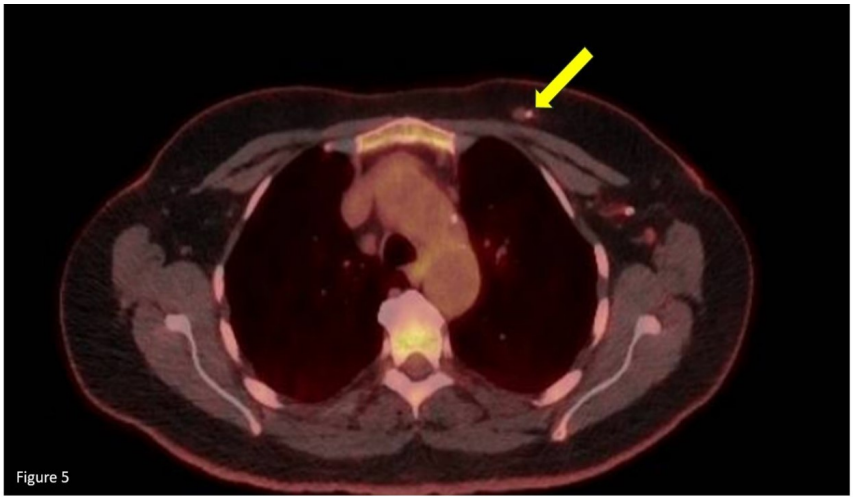

Figure 5

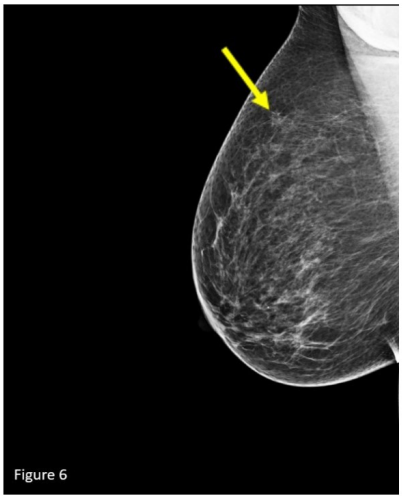

Figure 6

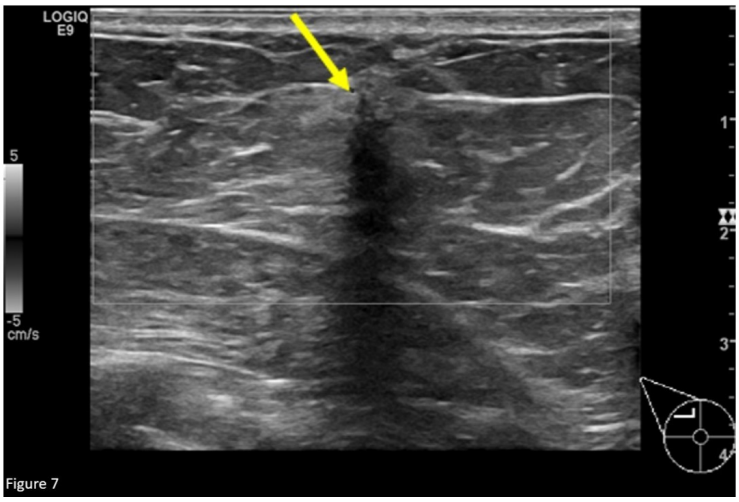

Figure 7

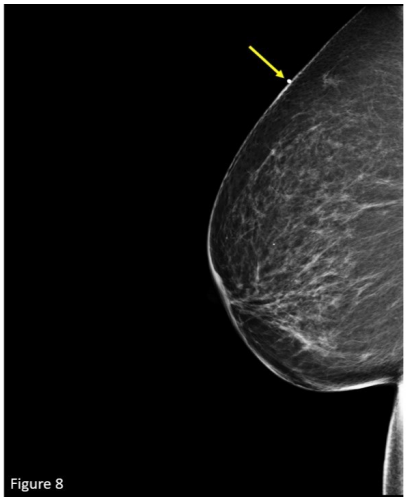
Figure 8

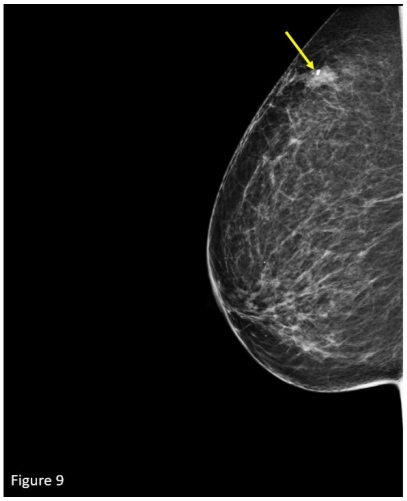
Figure 9