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Revisiting the Inscrutable Granular Cell Tumors in the Breast and Beyond: An Institutional Experience

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ABSTRACT

Background: Granular cell tumors (GrCTs) are rare neoplasms derived from Schwann cells and can affect any part of the body. They are histologically categorized into benign (most common), atypical, or malignant (<2%) subtypes.

Methods: A retrospective review of pathology-proven GrCTs at a tertiary hospital was done from 4/1/2014 to 3/31/2021. The patient age, gender, location of the tumor, and imaging findings were reviewed.

Results: A total of 18 patients with GrCTs were found over a period of 7 years. The sites of involvement ranged from the tongue to the heel. The most common site of occurrence was the esophagus. There were 2 cases of recurrences and 2 cases of multicentric GrCTs. In our study, we did not have atypical or malignant GrCTs.

Conclusion: Granular cell tumors are uncommon and primarily published as case reports and case series. Our seven-year review provides a comprehensive synopsis of this tumor in the breast and rest of the body. Their clinical and imaging features are non-characteristic, but histopathologic features with immunohistochemistry are diagnostic. Complete surgical excision with negative margins is the accepted standard of care. A global overview of this tumor will allow physicians to provide their patients with a better understanding of their diagnosis and prognosis.

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INTRODUCTION

Granular cell tumors comprise 0.5% of all soft tissue tumors.¹ They are distinctive from the granular cell changes that can occur in many neoplastic and non-neoplastic diseases. These tumors arise from Schwann cells and have a broad distribution in the body.

Epidemiology

GrCTs are more common in women, with up to two-thirds of cases affecting females.² They are also

more common in African Americans. It is a disease primarily afflicting adults but has also been reported in children and teenagers.² Commonly diagnosed in the second to sixth decades, they can occur at any age.^{3,4} They are usually solitary; only 5-10% are multiple.^{3,4} Malignancy is rare, <2%.²

Granular cell tumors are frequently subcutaneous, intradermal, or submucosal in location.⁵ (Figure 1).

Up to 40% GrCTs affect the head and neck region, most commonly the tongue, followed by 30% involving the skin and subcutaneous tissue.^{3,4,6,7} The gastrointestinal tract, chest wall, extremities, female anogenital region, larynx, bronchus, and pituitary gland are other sites of occurrence.^{3,8}

Rare locations include deep soft tissues, urinary bladder, scrotum, and vaccination scar sites.⁹⁻¹²

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Figure 1. Granular cell tumors are common in superficial locations. Submucosal location in the rectum (1a), subcutaneous location in the heel which recurred 4 years after resection (1b, 1c), and subcutaneous location in the forearm (1d).

The reported incidence of GrCTs in the breast ranges anywhere from 5% to 15%.¹³⁻¹⁶ They have also been found in the male breast, comprising 6.6% of all cases of GrCTs in the breast and with a reported 1:9 male to female ratio.^{2,17}

Clinical presentation

Patients usually present with a slow-growing, palpable, painless mass, with some complaining of pain or pruritis.³

Diagnosis and management

Although the vast majority are small tumors (<3cm), they can reach large sizes.^{1,18} Their clinical and imaging features are indistinctive, making their definitive diagnosis impossible without tissue sampling. Surgical management is the standard of care.

In this retrospective review, we analyzed all the cases of pathology-proven GrCTs at our institution. The objective of this study was to provide a concise

review of these tumors, with a special focus on their occurrence in the breast.

METHODS

This retrospective study was approved and deemed exempt by the Institutional Review Board of the University of Arkansas for Medical Sciences. Patient medical records were reviewed from April 1, 2014, to March 31, 2021. The pathology reports diagnosing GrCTs on core biopsy or surgical specimens were identified. The patient age, gender, race, tumor location, imaging characteristics, surgical outcome, and follow-up data (if available) were also obtained for these cases.

RESULTS

Over a period of 7 years, 18 patients were diagnosed with 19 GrCTs. The demographics and distribution of GrCTs within the body are shown in Figure 2.

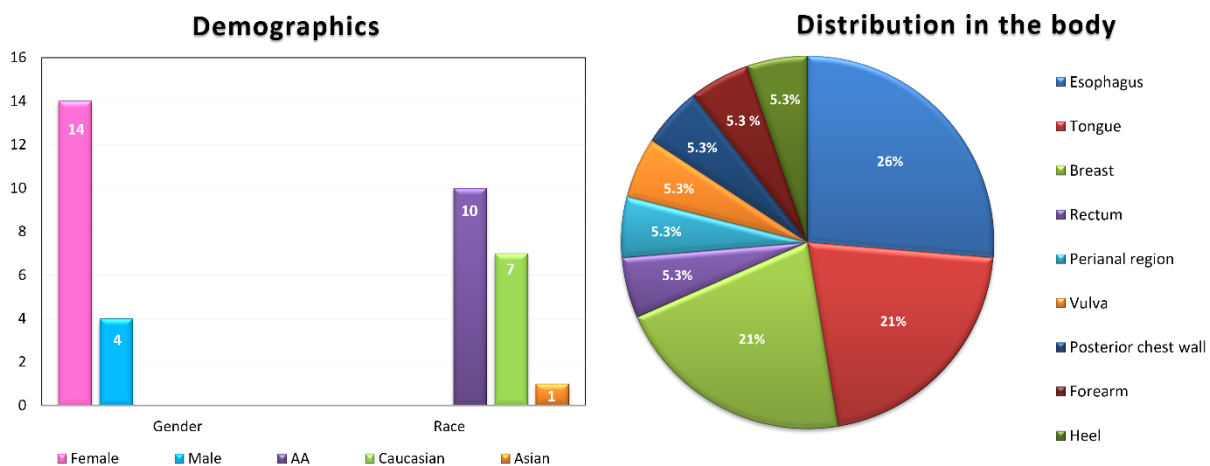


Figure 2. Gender, race, and location in the body of the patients with granular cell tumors.

The majority of the patients were female (78%) and African American (56%). The mean age at diagnosis was 47 years (range 23–70 years). The most common organ involved by GrCT was the esophagus (26%), followed by breast and tongue (both 21%).

The skin and subcutaneous tissues were the third most common site of involvement (16%, one in the posterior subcutaneous chest wall, one in the heel, and one in the forearm). The tumors ranged in size from 0.5cm to 6.6cm. The smallest tumor was in the tongue



and the largest in the subcutaneous posterior chest wall. We encountered two cases of recurrent GrCTs: one involving the breast and another the heel. Two patients had multicentric GrCTs: one patient with synchronous tumors in the breast and perianal region, another with metachronous tumors in the pancreas, spleen, and vulva. The patient with metachronous tumors was diagnosed with a GrCT in her vulva at our institute. She had previously undergone surgical resection of benign GrCTs in her pancreas and spleen at an outside hospital. All the GrCTs in our study were benign.

DISCUSSION

Granular cell tumors are distinctive in their ability to involve any part of the body; from the skin and subcutaneous tissue to the head and neck, gastrointestinal tract, and extremities. Given the rarity of these tumors, there is a wide variation in their reported prevalence and distribution in the body.^{8,13,14,19,20} Its tissue of origin has been a matter of long debate. It is now universally accepted that these tumors are of nerve sheath origin, as they are positive for S-100 protein and peripheral myelin proteins.³

History

A Russian pathologist, Dr. Alexei Abrikossoff, first fully described a GrCT involving the tongue in 1926.

Hence, they are sometimes referred to as Abrikossoff's tumors.²¹ Prior to that, it is believed Weber alluded to them in 1854.²² The tumors were initially thought to arise from the muscle, leading to misnomers like "granular cell myoblastoma", "myoblastic myoma" and "myoblastomas".^{6,13,21} Its present name, granular cell tumor, is derived from the presence of abundant granular eosinophilic cytoplasm in their cells.²³

Histopathology and Immunohistochemistry

These tumors are non-encapsulated.⁶ The characteristic histopathology of granular cell tumors is irregularly arranged, loosely infiltrating sheets of large, polyhedral cells containing abundant fine and coarse granular eosinophilic cytoplasm.^{6,7,24} (Figure 3).

On electron microscopy, the granular cytoplasm is found to be secondary to the accumulation of lysosomes, similar to those found in Schwann cells.²⁵ Although its granular cytoplasm is what leads to this tumor's name, it is a non-specific finding, also observed in many non-neural tumors.⁸

Immunohistochemistry is both diagnostic and helps identify clear surgical margins. These tumors are positive for S-100, CD68, and neuron-specific enolase.⁸ They stain negative for desmin, cytokeratins, and glial fibrillary acidic protein, helping to differentiate them from granular cell variants of other tumors.⁸

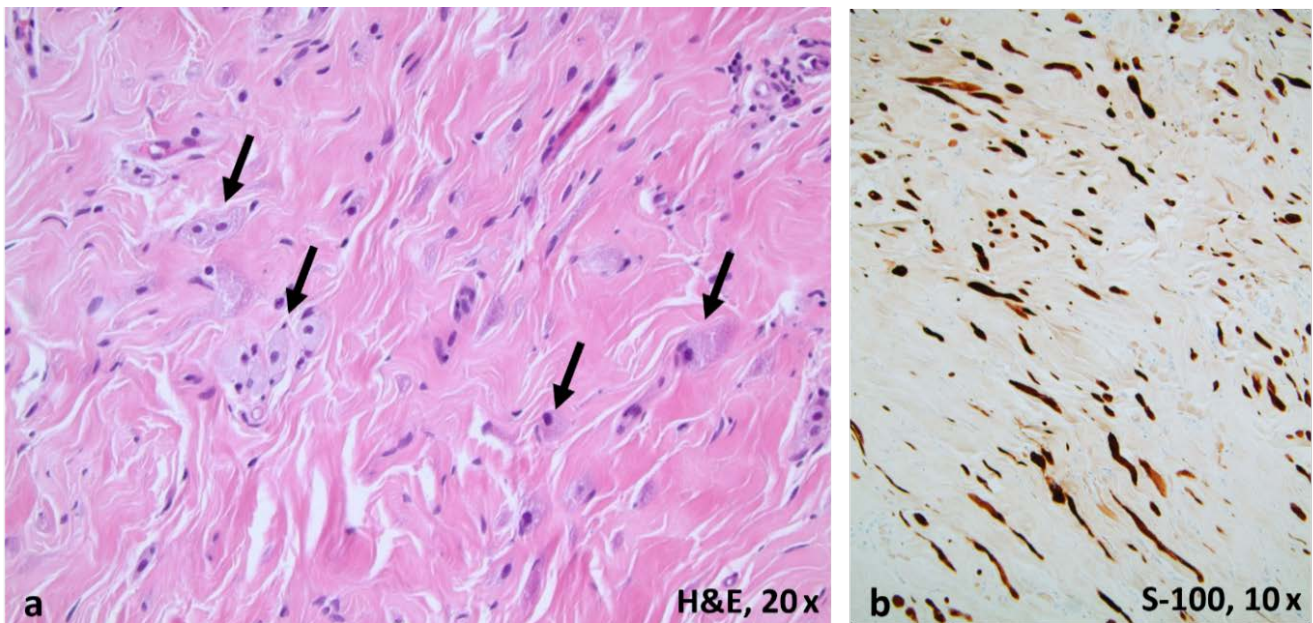


Figure 3. Histopathology. Granular cell tumor cells show an infiltrative growth pattern composed of cords of polygonal cells with distinct cell borders. The nuclei are bland, round to oval and the cytoplasm is abundant and granular (3a, Hematoxylin and Eosin (H&E) section). S-100 immunostain strongly highlights the neoplastic cells, supporting the diagnosis of granular cell tumor (3b). These cells are negative for keratin stain (not shown).

Fanburg-Smith *et al.* classified GrCTs into benign, atypical, and malignant categories based on six

histologic criteria (necrosis, spindling, vesicular nuclei with large nucleoli, increased mitotic activity, high



nuclear-to-cytoplasmic ratio, and pleomorphism).²⁶ Benign GrCTs have focal pleomorphism alone or none of the above criteria. Atypical GrCTs have 1-2 criteria and malignant GrCTs have 3-6 criteria. A higher Ki-67 proliferation index (>10%) and overexpression of p53 are also seen in atypical and malignant GrCTs. However, metastasis remains the sole conclusive criterion for malignancy.^{26,27}

Granular cell tumors overview

Similar to multiple prior studies, our study too found GrCTs to be more common in women (78%) and more common in African Americans (56%).² The mean age at diagnosis in our study was 47 years (age range of 23-70 years). The mean age range in literature is anywhere from the fourth to the sixth decades.^{3,4}

In our study, the esophagus was the most common site (5 cases, 26%). The next common sites of involvement in our study were the breast (4 cases, 21%) and the tongue (4 cases, 21%), followed by the skin and subcutaneous tissues (3 cases, 16%). This is unlike the study by Mobarki *et al.*, who reviewed 42 cases of GrCT over a period of 21 years and reported the skin and subcutaneous tissues as the most common sites of GrCTs.²⁸ Marcoval *et al.* reviewed 89 cases of GrCT in 81 patients over a period of 24 years and reported the skin and oral mucosa as the most common site of GrCTs.²⁰ Lack *et al.* also published similar findings; on reviewing 118 GrCTs over a period of 32 years, they found 44% of their cases occurred in the skin and subcutaneous tissue, although tongue was the single most common anatomic site in their study.⁴ The differences in the most common site of involvement are likely secondary to these studies spanning a longer period, and due to a difference in categorization of anatomic sites. Overall, the tongue, skin and subcutaneous tissues are the commonest sites involved by GrCTs.

Although involvement of the gastrointestinal tract is reported to be less common, approximately 5-6% of GrCTs,²⁹ this was the most common site in our study (5 cases in the esophagus and 1 case in the rectum). An *et al.* reviewed 98 cases of GrCTs of the gastrointestinal tract and reported esophagus as the most common site and no recurrence following surgical resection.²⁹ All the esophageal GrCTs in our study were diagnosed by endoscopy, underwent endoscopic resection, and are without recurrence for the span of our review.

These tumors demonstrate indolent growth as illustrated in Figure 4.¹³ In our study, we had a patient with a GrCT in her posterior chest wall, which only increased in size by 1.5cms over 11 years. She died at 36 years of age from chronic renal failure.

Multicentricity is a known feature of this tumor, reported being 5-10%.^{3,4} We had similar findings in our study, 2 patients (11%) had multicentric GrCTs, one with synchronous presentation, another with metachronous presentation. Marcoval *et al.* found that when GrCTs were multicentric, the patients were diagnosed at a younger age at the site of first involvement (21.6 years versus 41.4 years in patients with solitary GrCT).²⁶ However, in our study, both the patients with multicentric GrCTs were in the fifth decade when diagnosed at the site of first involvement.

Recurrence is another distinctive feature of this tumor and is discussed in the management section. Imaging features of GrCTs are non-specific. When imaged using intravenous contrast, regardless of tumor location, these tumors enhance. (Figure 5). GrCTs in the skin and subcutaneous tissues are not routinely imaged before biopsy. Similarly, GrCTs in the gastrointestinal tract are detected by endoscopy.²⁹ In the breast, initial imaging does not involve administration of intravenous contrast. The imaging features of GrCT in the breast are described in the section below.

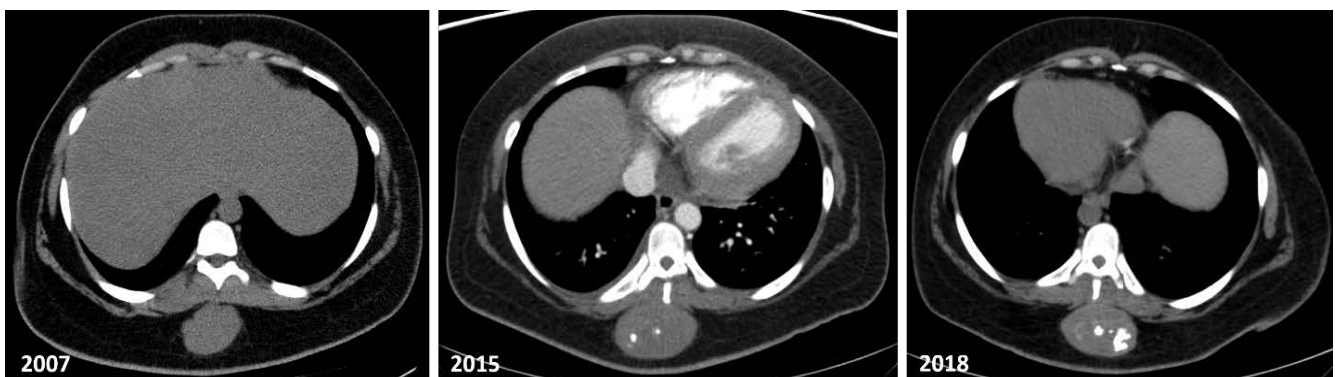


Figure 4. Slow growth: This 35-year-old patient presented with a painless, palpable, subcutaneous posterior chest wall mass in 2018, tissue sampling revealed a benign granular cell tumor. In retrospect, this tumor was present in a cross-sectional study dating back to 2007, with an incremental growth of 1.5cm spanning a period of 11 years. The progressive dystrophic calcifications within the mass were likely related to her chronic renal failure.

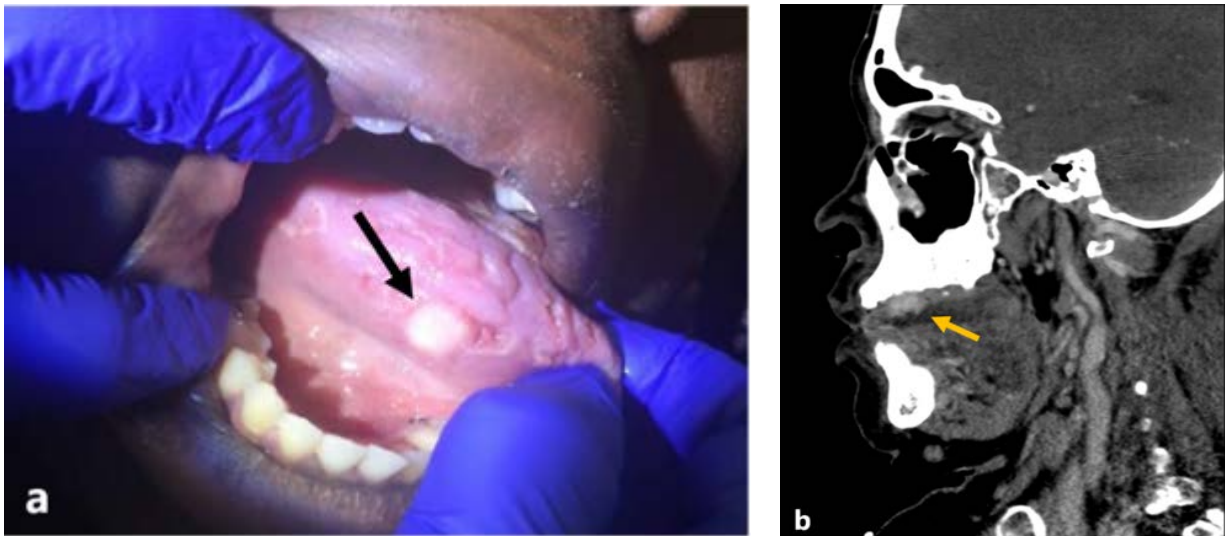


Figure 5. A 36-year-old female with granular cell tumor of the tongue (5a). Sagittal contrast-enhanced CT neck study revealed a non-specific homogeneously enhancing mass which is indistinguishable from tongue cancers (5b).

Granular cell tumor in the breast

Studies report that for every 1000 breast cancers diagnosed, 1-6.7 granular cell tumors are detected.^{2,30} It is commonly seen in premenopausal women and in African American women.² Despite their predominance in premenopausal women, they are not hormonally driven, as they lack estrogen and progesterone hormone receptors.² The youngest and oldest reported GrCTs involving the breast were in a 9-year-old premenstrual girl and an 83-year-old woman, respectively.^{5,31}

Many studies report preferential involvement of the right breast,¹⁵ but some do not state a laterality preference.² GrCTs were initially thought to be more common in the upper inner quadrant of the breast, driven by speculation that the cutaneous distribution of the supraclavicular nerve in this quadrant was the reason behind this propensity.^{14,32} However, GrCTs have been reported in every location in the breast, superficial and deep, from the axilla to the nipple.² They are slow-growing and painless, some presenting as palpable lumps while others are identified incidentally on mammography. Skin involvement (thickening, dimpling, and retraction) has also been reported.¹⁹

Granular cell tumors do not have characteristic features on any imaging modality. On mammography, they present as superficial or deep masses. Their morphology ranges from a round, oval, or irregular-shaped mass with circumscribed or non-circumscribed margins, with or without architectural distortion.^{2,31,33} Calcifications are rare.^{13,23} On ultrasound, they are hypoechoic or heterogeneous, with margins ranging from circumscribed to not circumscribed.^{2,31,33} (Figure 6).

Posterior acoustic shadowing may or may not be present. Anisotropy, the variation in echogenicity

based on the angle of insonation, is a unique feature of this tumor due to its internal fibrillary nature.¹⁹ (Figure 7).

Magnetic Resonance Imaging (MRI) is not normally a part of the initial workup of breast masses. In published literature where patients underwent a breast MRI, it has been found that GrCTs display variable enhancement following administration of intravenous gadolinium with persistent (type 1) to washout (type 3) kinetic curves.^{19,34} MRI can be a valuable tool in select patients, to determine the extent of disease, multicentricity, and involvement of the contralateral breast.

Overall, GrCTs in the breast have diverse imaging features and can mimic the appearance of benign lesions or scirrhous cancer in the breast. The lack of a tumor capsule and infiltrative nature can explain the aggressive imaging features of some GrCTs. They are usually designated anywhere from a BIRADS 3 to 5 category. The four cases of GrCTs in the breast in our study were assigned BIRADS 3 and 4 categories. The single patient assigned a BIRADS 3 category, later opted to undergo core biopsy, leading to her diagnosis of GrCT.

Tissue sampling, specifically core biopsy is diagnostic. Fine needle aspiration cytology is less sensitive and is not recommended.^{2,19}

Multicentric disease in the breast has also been reported.^{4,35} Multicentricity is favored to represent discrete primary tumors rather than metastasis as they did not have malignant features on histology.³⁵ It is also important to keep in mind that GrCTs can co-exist with malignant lesions.¹³

Although rare, it is worthwhile to keep a differential diagnosis of GRCT in mind for breast masses undergoing biopsies.

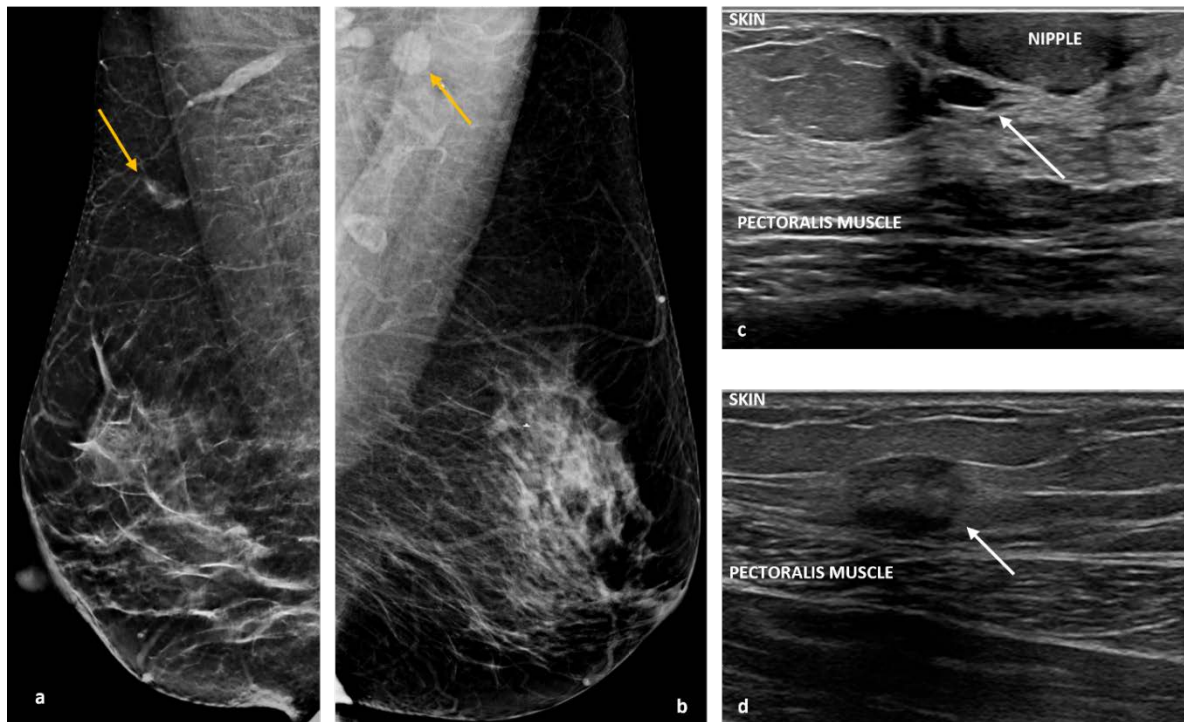


Figure 6. Imaging features of granular cell tumors in the breast on mammography and ultrasound: All different patients. Granular cell tumors can present as masses with non-circumscribed – (indistinct) margins (6a) or circumscribed margins (6b). Their location can be superficial - subcutaneous (6c) or deep, abutting the pectoralis major muscle (6d).

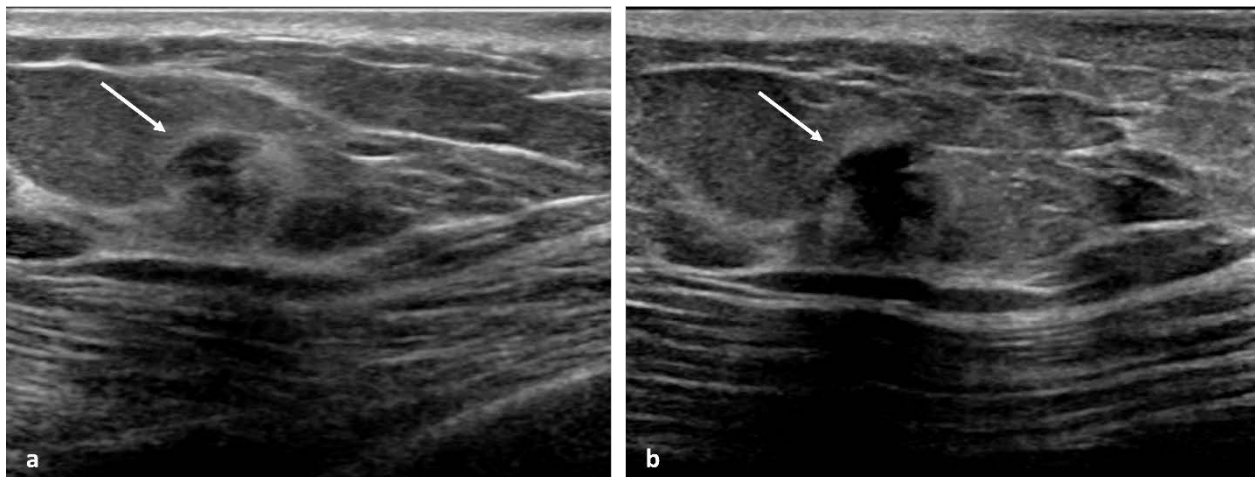


Figure 7. Anisotropy: Two serial ultrasound images in the radial orientation. The internal echogenicity of the granular cell tumor changes significantly with a small tilt of the probe.

Malignant granular cell tumors

Although we did not have a case of malignant GrCT in our study, we present the known and accepted features of malignancy for a complete perspective of this tumor.

Malignant GrCTs are aggressive. A clinical sign of malignancy is rapid growth.⁸ The commonly accepted imaging features of malignancy include the presence of pathologically enlarged lymph nodes, tumor size greater than 5cm, suspicious flow kinetics on contrast-enhanced MRI, and adjacent soft tissue infiltration.³⁶ Some studies regard a tumor size >4cm as suspicious for potential malignant GrCT.^{8,18,33}

Malignant GrCTs spread via lymphatics (to regional or distant lymph nodes) and hematogenous routes (to the liver, lungs, and bones).⁸ One study reported a 32% 2-year local recurrence for malignant GrCTs with a 50% rate of metastasis and a 39% 3-year mortality rate.²⁶ A more recent study of oral and cutaneous malignant GrCTs reported a 5-year survival rate of 62.8%.²⁰ One patient with metastatic GrCT of the anterior abdominal wall has survived 11 years from initial surgery with intermittent chemotherapy throughout her disease span.²⁷ Given the rarity of malignant granular cell tumors, their actual mortality rate is likely unknown.



Management

Regardless of the histological category, the treatment of choice in all GrCTs is surgical excision with wide margins, as positive margins increase the risk of recurrence.^{2,37,38} Sentinel lymph node biopsy is not recommended in benign or atypical granular cell tumors.^{37,38}

In certain circumstances, tumor location can preclude wide excision, such as proximity to the deep fascia and neurovascular bundles. Recurrence has occurred in cases with both clear and positive surgical margins.²⁶ The risk of recurrence is 2-8% with negative margins and 20% with positive margins.²⁶ However, recurrence of benign GrCTs does not portend a poor prognosis; they too have a good outcome.^{2,13} The risk of recurrence is believed to be higher with atypical GrCTs.³⁸

We had two cases of recurrent GrCTs with detection of recurrence at 2-year and 4-year intervals from their surgery (Figure 1b, 1c, 8). The patient with recurrence in the heel, went in for re-excision and is disease-free 4 years after his re-excision (Figure 1b, 1c). The patient with recurrent GrCT in the breast declined re-excision. Her recurrent tumor was stable on mammography for two years, after which she was unavailable to follow up (Figure 8). Given the indolent nature of these tumors, surveillance by imaging may be the best option in patients who decline surgical management.

There is no standardized recommendation for the frequency of clinical or imaging follow-up in post-surgical benign or recurrent cases of GrCT. Meani *et al.* recommend annual follow-up for at least 10 years.¹⁹

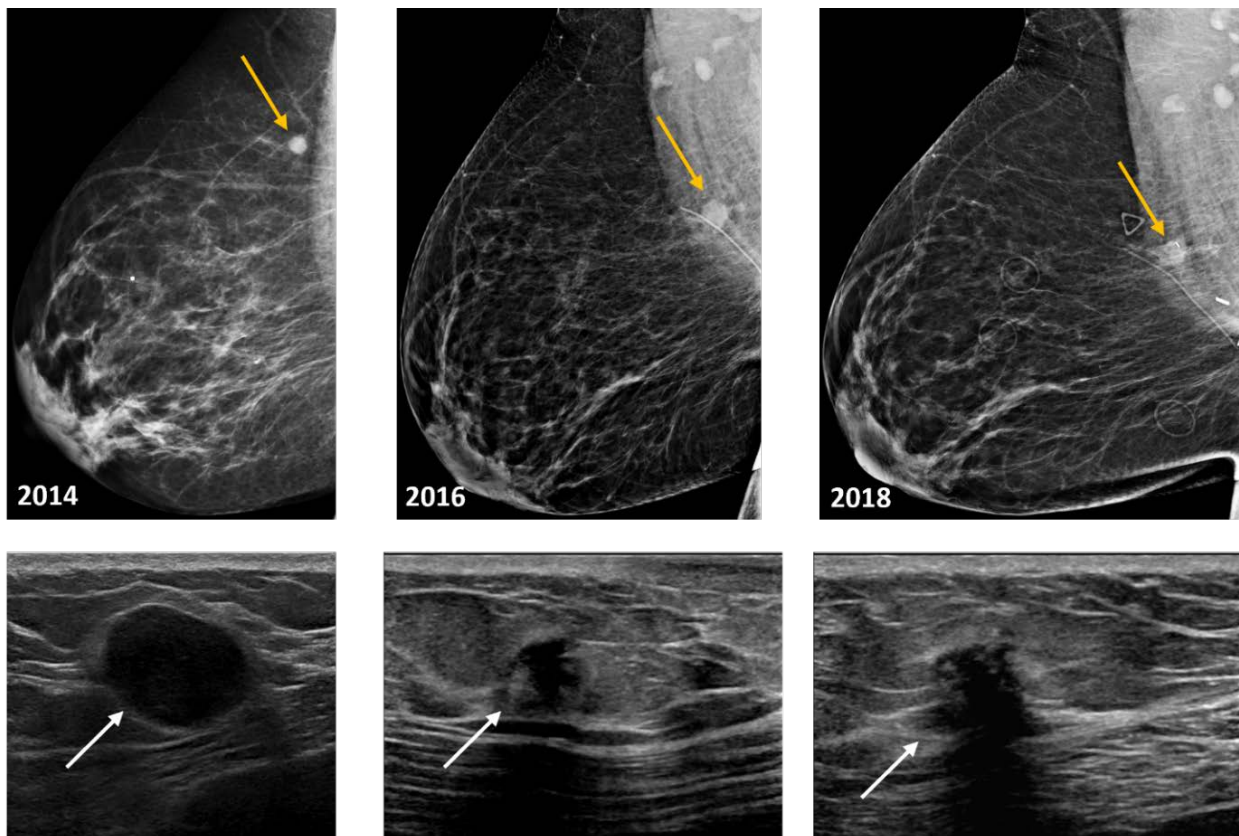


Figure 8. Recurrent granular cell tumor: A 47-year-old woman first presented in 2014 with a right breast palpable lump. On mammography, she had a 0.8cm round, circumscribed, equal density mass which was oval, parallel, circumscribed, and hypoechoic by sonography. She underwent surgical excision after her biopsy revealed a benign granular cell tumor. A recurrent 1.2cm mass in the surgical bed was found 2 years later. A repeat biopsy revealed recurrent granular cell tumor. The patient opted not to undergo a repeat surgical excision. The mass was stable in the 2018 mammogram. The patient was unavailable to follow-up as she relocated to a different state. The recurrent mass had non-circumscribed margins on mammography and sonography.

Malignant GrCTs require additional regional lymph node dissection. They have a poor prognosis with high rates of recurrence and a poor response to

chemotherapy and radiotherapy.^{8,26} Annual follow-up is recommended in these patients. There is a need for streamlined treatment and follow-up guidelines in this subgroup.



CONCLUSION

Granular cell tumors are mesenchymal tumors of Schwannian differentiation. They are unique due to their combined rarity and broad distribution. It is primarily a pathologic diagnosis without any distinctive clinical or imaging features. Hence, clinicians and breast radiologists alike are less familiar with all their characteristics. Having a global perspective of this tumor will enable physicians to confidently communicate with and educate their patients who receive this diagnosis. Although malignant GrCTs are rarer still, knowledge of their imaging criteria will ensure accurate documentation and staging. Wide

surgical excision with clear margins is the standard of care in all GrCTs.

ETHICAL CONSIDERATIONS

This retrospective study was approved and deemed exempt by the Institutional Review Board of the University of Arkansas for Medical Sciences.

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None.

CONFLICT OF INTEREST

The authors declare that they have no conflicts of interest.

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