

Granular Cell Tumour of Breast Mimicking Malignancy: A Series of Six Cases

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ABSTRACT

Granular Cell Tumour (GCT) of the breast is a rare, benign neoplasm of presumed Schwann cell origin, accounting for less than 0.1% of all breast tumours. Despite its benign nature and low recurrence risk, it often mimics malignancy both radiologically and histologically, leading to diagnostic uncertainty. This case series describes six histologically confirmed cases of breast GCT diagnosed over an 11-year period, highlighting key clinical, radiological, histopathological, and immunohistochemical features. All patients were women between 32 and 42 years, presenting with solitary, unilateral breast lesions. Radiological findings in several cases were suspicious for malignancy. Tumours ranged from 1 to 4.1 cm, frequently located in the medial quadrant, and exhibited ill-defined margins in most cases. Histologically, tumours were infiltrative and composed of polygonal cells with granular eosinophilic cytoplasm and round hyperchromatic nuclei. Periodic Acid Schiff-Diastase (PAS-D) positivity and positive immunohistochemical stains for S100 (solubility in 100% saturated ammonium sulfate at neutral pH), SRY-related HMG box 10 protein (SOX10), Transcription Factor Binding to IGHM Enhancer 3 (TFE-3), and Cluster of Differentiation 68 (CD68) positivity helped confirm the diagnosis. Common histological findings included adipose and skeletal muscle infiltration, peritumoural lymphocytic infiltrates, rare features such as intranuclear inclusions and stromal elastosis. No mitoses, necrosis, or co-existing carcinoma were noted. No recurrences or metastases were observed during follow-up. Given its ability to mimic malignancy, especially on core biopsies, GCT must be considered in the differential diagnosis of breast lesions with granular cytoplasm. Misinterpretation may lead to overtreatment. Awareness of its histopathologic profile and immunohistochemical signature is essential to avoid diagnostic pitfalls.

Keywords: Diagnostic pitfalls, Granular cell tumour, SRY-related HMG box 10 protein, Transcription Factor Binding to IGHM Enhancer 3

INTRODUCTION

GCT is a rare benign mesenchymal tumour, presumed to be of Schwann cell origin. It was first described by Abrikossoff in 1926. GCT occurs in various anatomical locations, with the tongue being the most common site. GCT accounts for approximately 0.1% of all breast neoplasms [1]. Despite its benign nature, GCT poses a significant diagnostic challenge due to its tendency to mimic invasive carcinoma clinically, radiologically, and histologically [1-4].

Clinically, these tumours often present as firm, irregular palpable masses, frequently raising suspicion of malignancy. Mammographic and sonographic features such as spiculated margins and irregular shape contribute to this confusion [2-4]. Histologically, GCTs are characterised by infiltrative growth, granular eosinophilic cytoplasm, and indistinct cell borders—features that may overlap with certain benign and malignant lesions. Also present are intracytoplasmic granules surrounded by clear halos called pustulo-ovoid bodies of Milian [1] [Table/Fig-1]. Accurate diagnosis relies heavily on histopathological examination supported by immunohistochemistry,

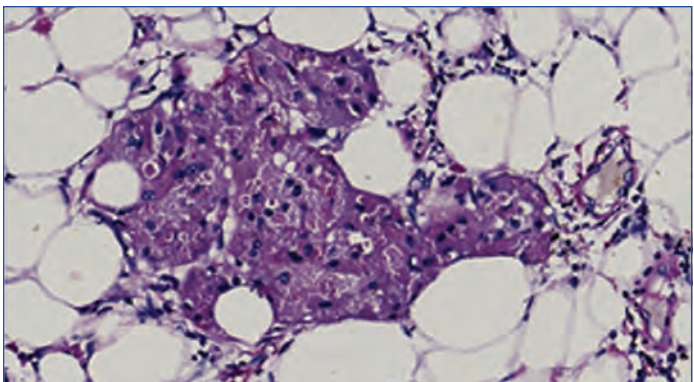
with tumour cells typically positive for S-100, SOX10, CD68, TFE3 and negative for cytokeratins [3,4].

Failure to correctly identify GCT may lead to unnecessary aggressive surgical interventions or overtreatment. By highlighting key diagnostic pitfalls, we seek to raise awareness of this rare tumour and emphasise the importance of recognising its mimics in order to avoid misdiagnosis [4]. Six cases of histologically confirmed GCT of the breast diagnosed between January 2014 and December 2024 were retrieved from the electronic database of the Pathology department. Five of the six cases were from patients diagnosed in this hospital, and only one case was a slide and block from outside for review. Clinical, radiological, histological, and immunohistochemistry were studied in all cases.

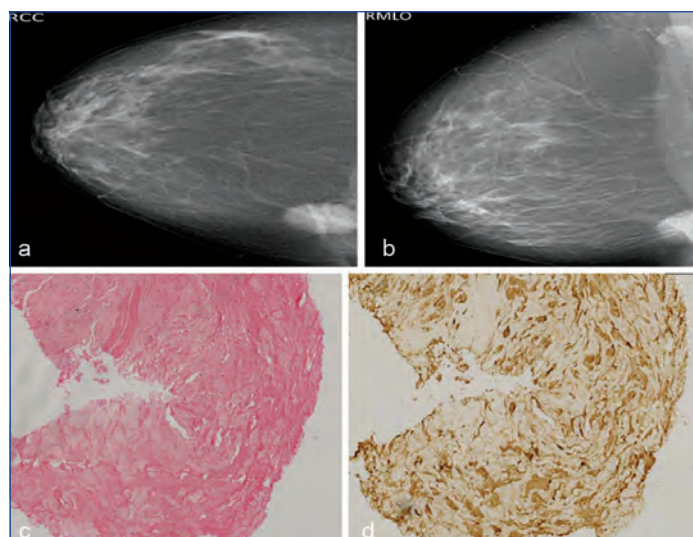
Case 1

A 41-year-old female patient presented with a right breast lump that had been present for 10 years. Her medical history was unremarkable, and there was a negative family history of breast and ovarian cancer. On physical examination, a hard lump measuring 3×4 cm was palpable in the lower inner quadrant of the right breast at the 4 o'clock position, with no palpable lymph nodes. The contralateral breast and axilla were normal. A mammogram showed a spiculated high-density lesion measuring 3.9×3 cm in the lower inner quadrant of the posterior third of the breast. Ultrasound demonstrated similar features with attachment to the deeper structures, classified as Breast Imaging-Reporting and Data System (BIRADS) -5. A subsequent core biopsy of the breast lump confirmed the diagnosis of GCT based on histology supported by immunohistochemistry [Table/Fig-2].

Wide local excision two months later revealed a unifocal, ill-defined grey-white tumour macroscopically. Additional histopathological features included extension up to the subareolar region, stromal

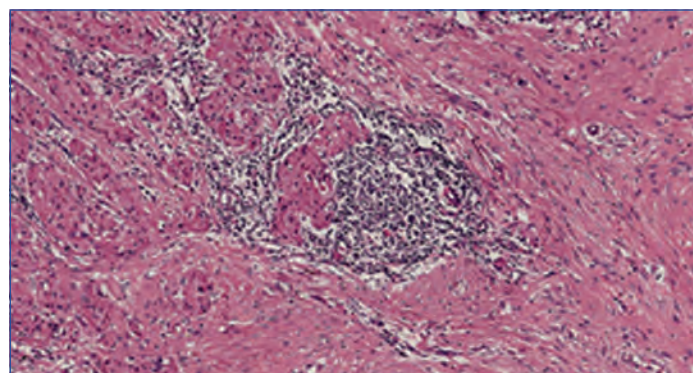


[Table/Fig-1]: PAS-D staining highlights the Pustulo ovoid bodies of Milian [400x].



[Table/Fig-2]: Case 1: a & b) Mammography: A high density oval shaped mass with spiculated margin in the posterior third aspect of inner lower quadrant of right breast; c) Granular cell tumour (Haematoxylin and Eosin (H&E) 100x); d) S100 (cytoplasmic staining) (100x).

sclerosis, and infiltration into the skeletal muscle fibers and adipocytic tissue. Peritumoural lymphocytes were present [Table/Fig-3]. It was a straightforward diagnosis with no differentials. The patient did not have local recurrence or distant metastasis on follow-up after six months.



[Table/Fig-3]: Peritumoural lymphocytic infiltrates.

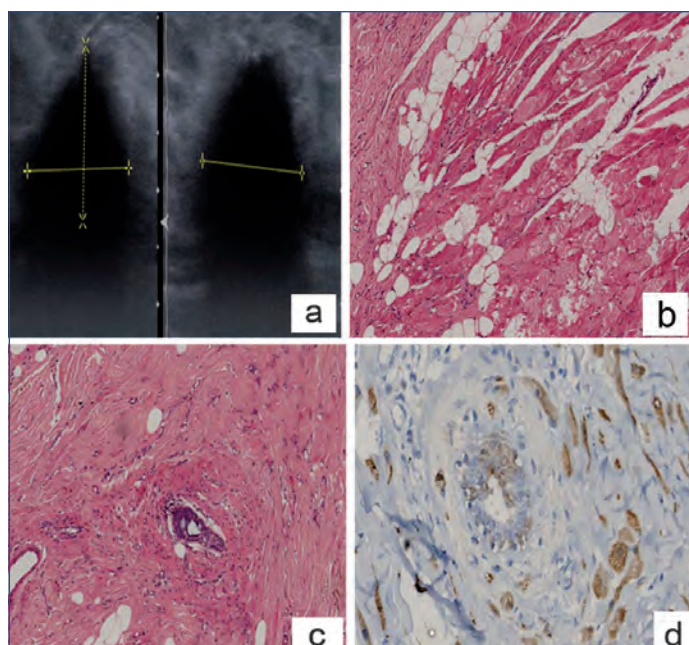
Case 2

A 33-year-old female presented with a non-progressive, painless left breast swelling that was present for 16 years. She was clinically suspected to have a chondroma at a center outside. Her medical history was unremarkable, with no positive family history of cancer. Examination revealed a firm lump measuring 3x2 cm with restricted mobility, palpable in the upper inner quadrant of the left breast. There were no palpable lymph nodes, and the contralateral breast and axilla were normal.

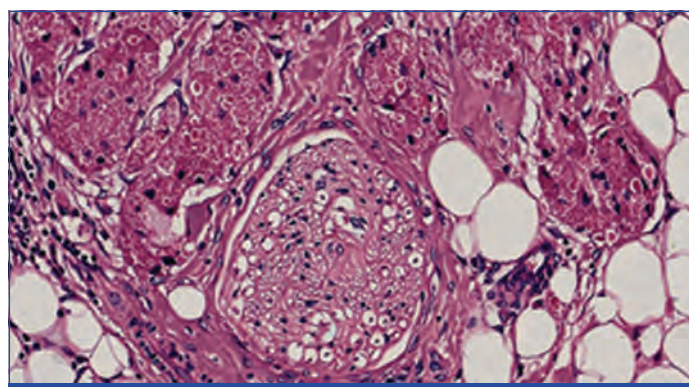
Ultrasound showed an ill-defined, taller-than-wide lesion at the 9 o'clock position measuring 1.9x1.8 cm; the posterior extent was not seen due to posterior acoustic shadowing, classified as BIRADS 5. Mammography displayed similar findings. A core biopsy was performed, but the tumour was missed due to the densely sclerotic stroma and adipocytes. The tumour was identified as singly dispersed cells entrapped within the stroma, which was only recognized retrospectively. Upon wide local excision, a 2 cm firm mass displayed similar histological features, further confirmed by immunohistochemistry [Table/Fig-4]. The tumour was seen surrounding nerve bundles, although peritumoural lymphocytes were not evident [Table/Fig-5]. The patient was advised to return for a six-month review but was lost to follow-up.

Case 3

A 32-year-old woman presented with a progressively enlarging right breast lump, first noticed 10 months prior, with no family history of



[Table/Fig-4]: Case 2: a) Markedly hypoechoic lesions with posterior acoustic shadowing at 9 o'clock position of left breast. Granular Cell Tumour (GCT) surrounding a duct; (b) and infiltrating the skeletal muscle fiber and adipose tissue in: (c) (H&E 100x); d) Immunohistochemistry highlights cytoplasmic staining of S100 (100x).



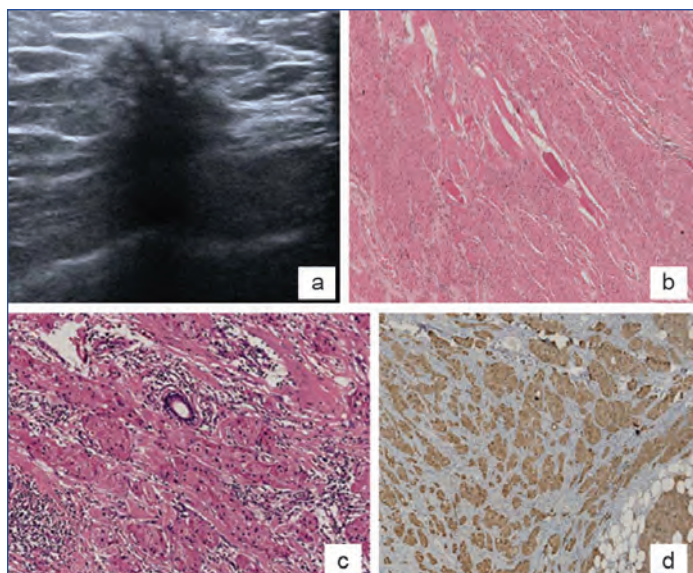
[Table/Fig-5]: Tumour surrounding the nerve [400x].

cancer. She had previously tried homeopathic remedies. Examination revealed a firm swelling measuring 2x3 cm with restricted mobility, located 2 cm away from the parasternal region. The contralateral breast and axilla were normal. An ultrasound showed an ill-defined hypoechoic lesion with irregular margins in the right parasternal region at the 1 o'clock position, measuring 19.5x18.8 mm. The patient underwent a Computed Tomography (CT) scan to identify the epicentre of the tumour, which revealed an irregular nodular lesion seen in the inner quadrant of the right breast with infiltration of the underlying pectoralis major muscle, suspicious for malignancy.

A core biopsy confirmed the diagnosis of GCT, and the patient subsequently underwent lumpectomy. Macroscopically, it was a unifocal, well-circumscribed 2x2 cm grey-white tumour. In addition to the granular cell morphology, some striking features included skeletal muscle infiltration, surrounding a nerve bundle, and breast lobules and ducts. Peritumoural lymphocytic infiltrates were seen within a desmoplastic and elastotic stroma [Table/Fig-6]. The patient was followed up after a year with no swelling on examination, but ultrasound identified a BIRADS IVa lesion, which on biopsy was found to be a fibroadenoma. She remains asymptomatic and is under annual surveillance.

Case 4

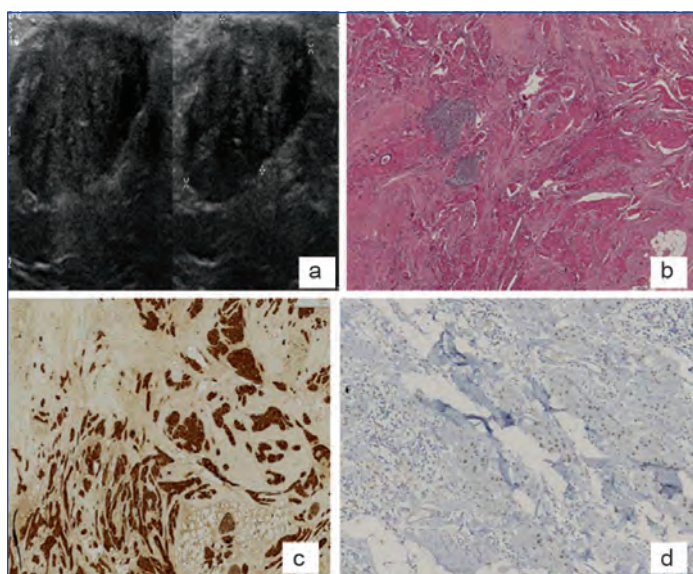
A 34-year-old female presented with an accessory breast lump that had been painless and non-progressive for three years. She had been diagnosed with ductal carcinoma on fine needle aspiration cytology performed elsewhere. There was no family history of



[Table/Fig-6]: Case 3: a) An ill-defined taller than wider hypoechoic lesion with irregular margins seen medial to right 1 o'clock position in the right parasternal region. Granular Cell Tumour (GCT) infiltrating the skeletal muscle fibers (b), surrounding the ducts with peritumoural lymphocytic infiltrates (c) (H&E 100x); d) Immunohistochemistry for S100 (100x).

cancer. Examination revealed a firm lump measuring 4x3.5 cm beneath the skin in the accessory breast. There were no palpable lymph nodes or contralateral breast involvement.

An ultrasound showed a well-defined, lobulated hypoechoic lesion in the left accessory breast, classified as a BIRADS 4B lesion. Core biopsy demonstrated tumour cells with abundant eosinophilic cytoplasm, and differential diagnoses of apocrine carcinoma and GCT were considered. The tumour exhibited mild pleomorphism and inconspicuous nucleoli, which, alongside immunohistochemistry, further supported a diagnosis of GCT. She underwent lumpectomy, which macroscopically revealed a unifocal, well-circumscribed grey-white lesion. Additional histological features observed included subareolar location, stromal elastosis, and dense peritumoural lymphocytic infiltrates [Table/Fig-7]. She was asked to return after six months but failed to follow up.

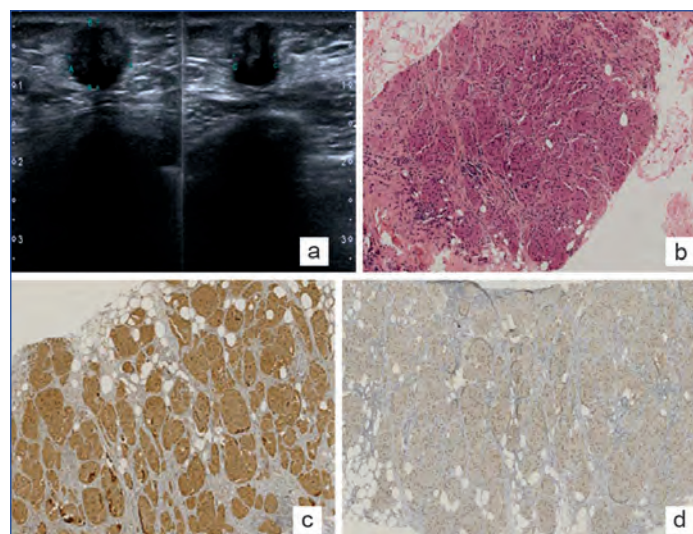


[Table/Fig-7]: Case 4: Granular Cell Tumour (GCT) (H&E 100x); a) An oval shaped intermediate density mass with partly circumscribed and partly spiculated margins in the accessory breast region of left axilla; b) shows granular cell tumour and focal peritumoural lymphocytic infiltrates (10x); c) Immunohistochemistry for S100 (cytoplasmic); (d) and moderate to faint nuclear staining for TFE3 (100x);

Case 5

A 33-year-old female was evaluated for a right breast mass of unknown duration, suspected to be mastitis. Her medical history was unremarkable, and there was a negative family history of breast and

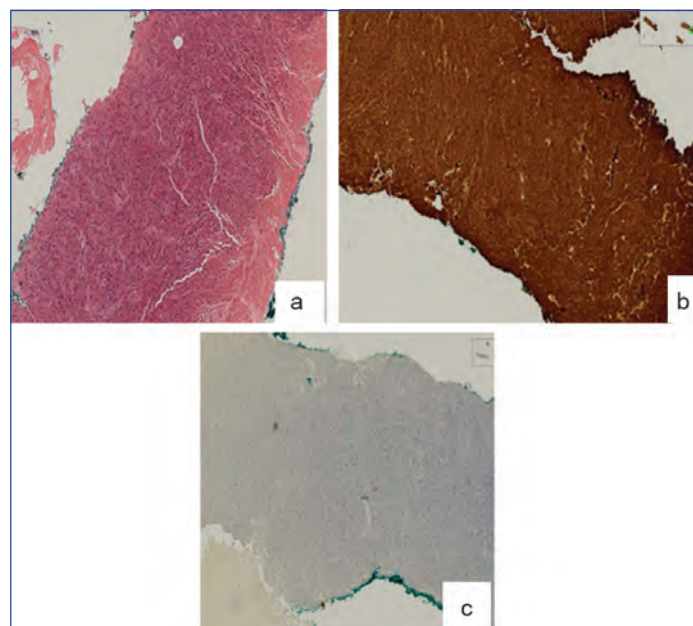
ovarian cancer. Examination revealed a hard lump measuring 2 cm in the upper outer quadrant of the right breast. Ultrasound showed a 1 cm BIRADS 4B lesion in the same quadrant. The patient was diagnosed with GCT, showing diffuse staining for S100 and TFE-3 on core biopsy. Peritumoural lymphocytic infiltrates were observed [Table/Fig-8]. The patient did not opt for excision and was lost to follow-up.



[Table/Fig-8]: Case 5: a) Well-defined hypoechoic wider than taller mass lesion with punctate calcific foci having no significant internal vascularity, causing posterior acoustic shadow noted at 10 o'clock position in outer aspect of right breast; b) Core biopsy with nests of Granular Cell Tumour (GCT) (H&E100x); c) Immunohistochemistry for S100; d) and TFE3 (diffuse faint nuclear staining).

Case 6

A 44-year-old female presented with an incidentally detected lump and nipple discharge of several weeks' duration and underwent core biopsy elsewhere. The radiological and clinical details of the patient were unavailable. Histology showed GCT in sheets with diffuse positivity for S100 and negative results for cytokeratin. Peritumoural lymphocytic infiltrates were not present [Table/Fig-9]. The adjacent breast also showed columnar cell changes. The patient did not wish to continue treatment here, so follow-up data is not available.



[Table/Fig-9]: Case 6: a) Core biopsy with Granular Cell Tumour (GCT) arranged in sheets (H&E100x); b) Immunohistochemistry in (b) highlights diffuse cytoplasmic staining for S100 and CK is negative within the tumour in (c) (100x).

DISCUSSION

Although the breast is not the most common site for GCT, it accounts for 8% of all cases [1], which in our series represented 12.7%. The average age in this series is 35.8 years, while other studies have reported an average age of 40 years [5]. GCT is most

often seen in middle-aged, premenopausal women, which aligns with our study [1]. Reports of GCT in the male breast are rare; notably, our study did not identify any such cases [6]. The average tumour size radiologically is approximately 2.18 cm, consistent with literature, while histopathologically it is 2.6 cm, ranging from 2 to 3.6 cm, similar to the study by Adeniran A et al., [7].

GCT is thought to arise most commonly from the superomedial quadrant of the breast, in proximity to the supraclavicular nerve, which is postulated to have a neural derivation [8]; this was observed in 3 out of 6 of our cases. Tumours are usually unicentric, which concurs with our series [1]. GCT can coexist with in-situ or invasive ductal carcinoma in the ipsilateral [8] or contralateral breast; however, there were no such cases in our study [9].

Imaging typically reveals an irregular, non-calcified mass with spiculated margins and high density on mammography, along with marked posterior acoustic shadowing on ultrasound—features that can mimic malignancy. Similar imaging characteristics were observed in five cases in our study. The tumour was most often excised due to suspicion of malignancy, both clinically and radiologically [2]. GCT typically has infiltrative borders and is arranged in sheets, clusters, and trabeculae, or as singly lying polygonal cells with indistinct cell borders that appear syncytial in many areas. The round hyperchromatic nuclei can vary in size, and nucleoli can range from absent to distinct. The cytoplasm is usually abundant, granular, and eosinophilic [1]. The Pustulo-Ovoid bodies of Milian were noted in almost all cases [10].

The tumour involved the skeletal muscle fibres and surrounded small-sized nerve bundles. There was no recurrence in any of the tumours, which is consistent with many studies [5]. There were no malignant or hereditary cases in our series [9]. Tumour-infiltrating lymphocytes were observed in four cases (66.67%), suggesting an immune response to the tumour. The lymphoid infiltrates were small, well-circumscribed, and lacked lymphoid follicles with germinal centres. Comparable findings have been reported in GCTs of soft tissue [11]. Immunohistochemistry performed on these tumours was positive for S-100, CD68, SOX10, TFE3, and negative for cytokeratin [1,11].

Pathologists must be aware of the various pitfalls in the microscopic diagnosis of GCT of the breast. The tumour can be very subtle and may be missed on core biopsies, especially if individual tumour cells have ill-defined borders and are lying singly, as was reported in one of our cases. The bland neoplastic cells can be mistaken for macrophages, misdiagnosed as an abscess, histiocytic reaction in fat necrosis, or histiocytic tumour. CD68, a macrophage marker that is commonly positive in GCT, compounds this difficulty [3]. Additionally, when GCT occurs near the subcutis, the previously mentioned differentials, along with rhabdomyoma, melanoma, and granular variant of squamous cell carcinoma, must be considered [4].

More dangerous is when the infiltrating tumour cells are mistaken for carcinoma of the apocrine type, as both tumours exhibit abundant granular eosinophilic cytoplasm. Hormone receptor studies are often triple-negative in apocrine carcinoma, which can also lead to misdiagnosis. Apocrine carcinoma cells typically display much more nuclear pleomorphism and prominent nucleoli. The lack of these morphological features, combined with negativity for cytokeratin, aids in reaching the correct diagnosis [4].

Alveolar Soft Part Sarcoma (ASPS) poses a major diagnostic dilemma, as these two tumours can be difficult to distinguish in some cases, and the management differs for each. Immunohistochemistry for TFE3 can be positive in both tumours. ASPS has a highly vascular stroma containing thin-walled vascular channels, which are lacking in GCT. In all cases of GCT, PAS-D highlights the coarse granules and demonstrates S100 positivity [12]. Recent studies have identified inactivating mutations in vacuolar H-ATPase genes—most commonly ATP6AP1 and ATP6AP2—as drivers of GCT [13]. In this study, molecular profiling was not performed. Although rare, GCT is associated with several syndromes, which were not observed in this series [1]. GCT is a benign entity with negligible recurrence rates following excision, even if margins are positive.

CONCLUSION(S)

GCTs of the breast are rare benign neoplasms that can clinically and radiologically mimic malignant breast lesions. Histopathological examination, aided by immunohistochemistry, is essential for accurate diagnosis. Awareness of GCTs and their distinguishing features, as well as diagnostic pitfalls, is crucial to avoid misdiagnosis and unnecessary interventions. GCT is not merely a malignancy mimicker but also a histological imitator. The presence of peritumoural lymphocytic infiltrates and stromal elastosis, observed in the majority of our cases, may reflect an ongoing host immune response, though their prognostic significance remains unclear.

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