

**Case Report**

# Rare Breast Granular Cell Tumor with Alpha-1 Antitrypsin Expression: A Case Report and Literature Review

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**Breast granular cell tumors are rare benign tumors with clinical and radiological resemblance to mammary carcinoma. Definitive diagnosis usually needs tissue or fine needle aspiration based cellular examination. Special stains, including PAS, PASD, S-100 and CK, are very important for reaching the correct diagnosis. However, the current markers to differentiate this tumor from histiocytes, including  $\alpha$ -1-antitrypsin,  $\alpha$ -1-antichymotrypsin and CD68, are not very specific. Both  $\alpha$ -1-antitrypsin and CD68 are positive in our case. A more extensive panel of histiocytic markers should be tested to evaluate their differential utility between histiocytes and GCTs, especially breast GCTs.**

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**Key Words:** breast granular cell tumors (GCTs); alpha-1 antitrypsin, immunohistochemistry, literature review

## INTRODUCTION

Granular cell tumors (GCTs) were first described by Abrikosoff in 1926 as a “myoblastic myoma”, which was considered as a “striated muscle cell tumor”.<sup>1</sup> However, later immunohistological and ultrastructural studies demonstrated that these tumor cells are more likely derived from Schwann cells of the peripheral nerves.<sup>2</sup> GCTs may occur in multiple sites throughout the body, but oral cavity, particularly tongue is the most frequent sites, followed by soft tissues.<sup>2,3,4</sup>

Breast GCTs are rare tumors, only accounts for 5-8% of all GCTs. Usually, breast GCTs present as solitary, slow growing, painless firm nodular lesion, often fixed to the skin, and “rock hard”. Multiple (multifocal) or bilateral lesions have been reported in 5.4% to 17.6% of the cases. GCTs, particularly the multifocal type, tend to be more common in African American population. They may occur in both sexes, but are slightly more common in female. Even though most cases of breast GCT are benign, they can closely simulate breast cancer on image study and clinical examination.<sup>3,4</sup> Without histological examination, it is always a challenge to make correct diagnosis.

Herein, we describe a new case of breast GCT in a 46 year old woman, with strong expression of alpha-1 antitrypsin, which is an uncommon feature for breast GCTs, and a brief review of the literature.

## CASE REPORT

This is a 46 year old African American female presented to our clinic with complaint of a firm mass in her right breast. Physical examination revealed a 25 mm painless palpable

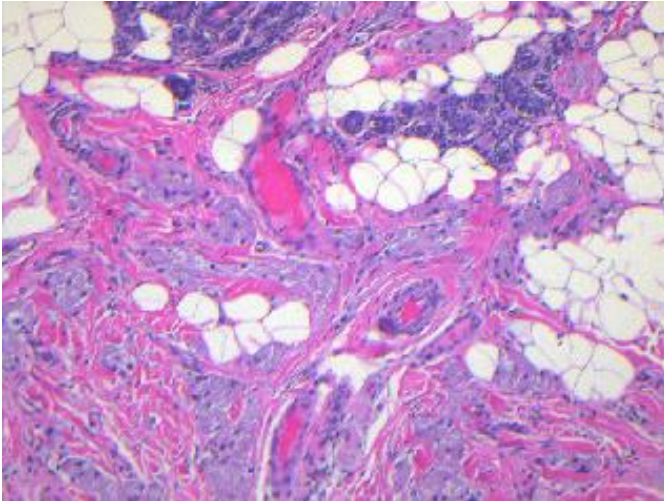
mass in the right upper outer quadrant, with skin retraction and nipple inversion. Mammography showed a 25 mm diameter infiltrative solid mass. Based on these findings, the mass was clinically diagnosed as malignant mammary cancer and lumpectomy was scheduled. An intraoperative frozen section biopsy and pathological consultation were requested.

Frozen section biopsy of the mass revealed small nests and infiltrating bland polygonal cells. The cells showed rich cytoplasm and round nuclei with prominent nucleoli. No nuclear pleomorphism or mitosis was identified. Numerous eosinophilic cytoplasmic granules were identified in most tumor cells. Frozen section diagnosis was: suggestive of granular cell tumor, no evidence of malignancy. Another subcutaneous frozen section biopsy was submitted, and an identical diagnosis was rendered.

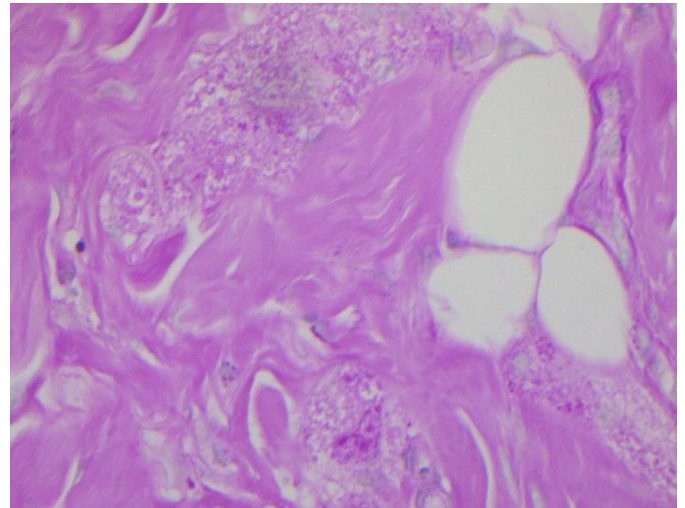
Gross examination of the lumpectomy sample revealed a grey-white, ill-defined firm to hard nodular lesion, cut surface showed a homogenous grey-white texture. The tumor was focally extending into the adjacent breast parenchyma. Microscopic examination showed clusters of polygonal tumor cells with eosinophilic granular cytoplasm infiltrate between collagen bundles and breast parenchyma (**Figure 1**). The cell borders were well-defined and normal nuclear-cytoplasm ratio was noted. The tumor cell nuclei are round with open chromatin and prominent nucleoli. The final diagnosis of granular cell tumor of breast was supported by subsequent PAS-D staining (**Figure 2**) and immunohistochemical examination, which showed that S-100 protein (**Figure 3**), Neuron Specific Enolase,  $\alpha$ -Inhibin (**Figure 4**), and CD68 (**Figure 5**) are positive; keratin and ER/PR are negative. Interestingly, this tumor is also strongly positive for  $\alpha$ -1-antitrypsin (**Figure 6**), which is an uncommon feature for breast granular cell tumors.

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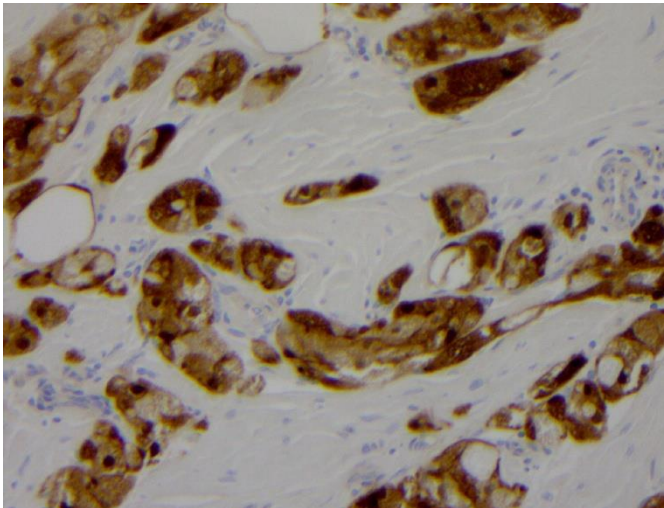
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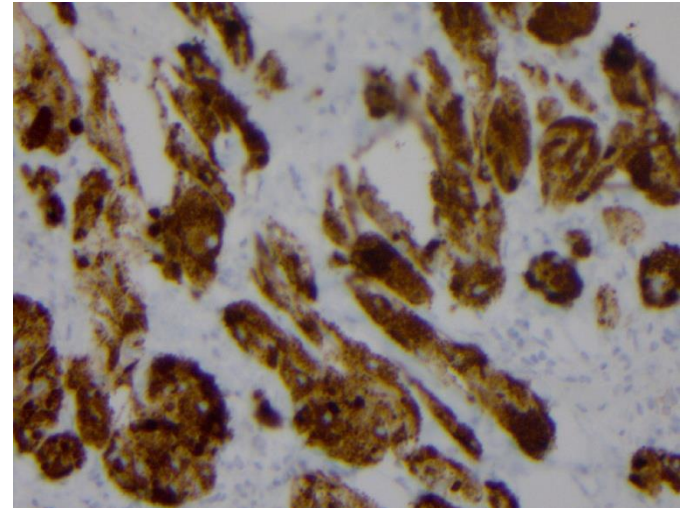
**Figure 1.** Clusters of polygonal tumor cells with eosinophilic granular cytoplasm, infiltrate between collagen bundles (H&E, original magnification, X 200).



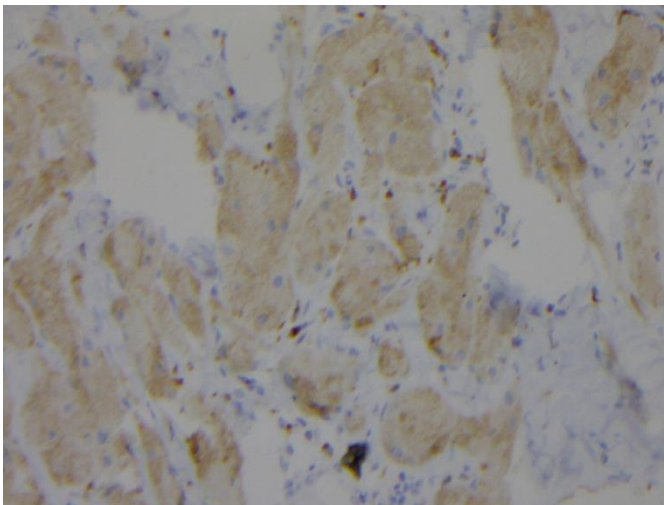
**Figure 2.** The prominent cytoplasmic granule staining by PAS after diastase digestion. (Original magnification, X 400).



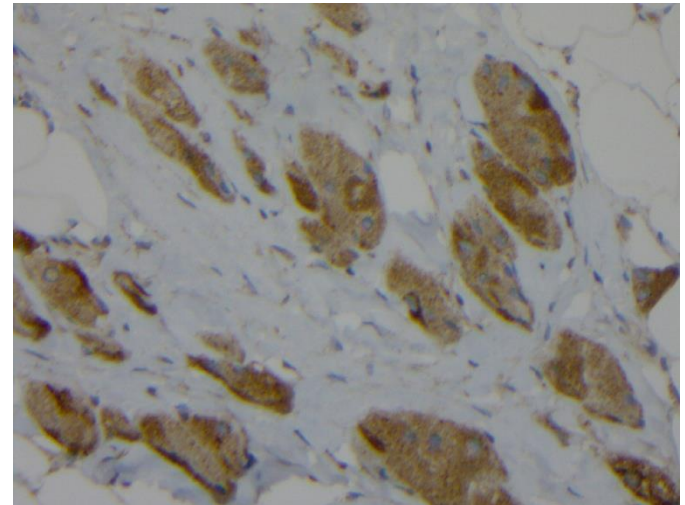
**Figure 3.** The typical nuclear and cytoplasmic stain for S-100 in the tumor cells. (Original magnification, X 100).



**Figure 4.** GCT cells are strongly  $\alpha$ -inhibin positive. (Original magnification, X 400).



**Figure 5.** GCT cells show variable cytoplasmic CD 68 positivity. (Original magnification, X 400).



**Figure 6.** GCT cells are strongly alpha-1-antitrypsin positive. (Original magnification, X 400).

## DISCUSSION

Breast GCTs are rare tumors. Most pathologists believe that breast GCTs are originated from the Schwann cells between the lobular breast parenchyma.

Although GCTs are usually benign in nature, they can closely resemble the malignant breast carcinomas on image and clinical exam. They are always nightmares for patients unless the correct diagnosis is made, which depends entirely on pathological examination after biopsy or excision. On physical examination, GCTs usually manifest as painless, firm and palpable masses, typically less than 3 cm in size.<sup>2-5</sup> They may cause skin retraction, infiltration, or ulceration, all features that mimic the malignant breast cancers. Ultrasound and mammography features that are suggestive of invasive ductal carcinoma or ductal carcinoma in situ including ill-defined or spiculated lesions, as well as microcalcifications. Microcalcifications are not common findings in GCTs.<sup>15</sup> In difference to most other breast tumors, which occur primarily in the upper outer quadrant, most breast GCTs occur in the upper inner quadrant, which corresponding to the sensory distribution of the supraclavicular nerve.<sup>3,4</sup> But in our case, the mass was in the upper outer quadrant, with skin retraction and nipple inversion, which make the diagnosis even more difficult. Histologically, GCTs can usually be differentiated easily from mammary carcinomas. GCT cells are bland, polygonal, forming nests and sheets. GCTs do not contain mucin, and do not react with cytokeratin or EMA.

One interesting feature of our breast GCT is its strong positive staining of  $\alpha$ -1-antitrypsin. On routine H&E preparation, GCTs are sometimes confused with histiocytic tumor, or simply benign histiocyte aggregates. Several immunohistochemical markers, including  $\alpha$ -1-antitrypsin and  $\alpha$ -1-antichymotrypsin, have been suggested as specific markers for histiocytes, especially in the breast.<sup>6,7</sup> However, the tumor cells in our case strongly express  $\alpha$ -1-antitrypsin. It has been suggested GCTs might be a heterogenous population with different cellular origin. For example, in a study published in 1987, one out of 8 GCTs was positive for  $\alpha$ -1-antitrypsin and  $\alpha$ -1-antichymotrypsin.<sup>8</sup> In another study, 10 GCTs, either adult or congenital type, were positive for  $\alpha$ -1-antitrypsin.<sup>9</sup> CD68, another commonly used histiocytic marker that labeled a protein closed related to  $\alpha$ -1-antitrypsin, is also positive in our case.

Although many studies suggest that positive immunoreactivity for  $\alpha$ -1-antitrypsin and CD68 in GCT may be a reflection of intracytoplasmic accumulation of phagolysosomes, not an indication of histiocytic origin for this tumor,<sup>9</sup> our results raise the possibility of different cell origin (s) or tumor differentiation in the granular cell tumor of the breast. We suggest a more extensive panel of histiocytic markers been tested in more human samples to evaluate their differential utility between histiocytes and GCTs, especially breast GCTs.<sup>10</sup>

Most (> 99%) GCTs are benign, only less than 1% of all GCTs are malignant.<sup>11</sup> Malignant GCTs are considered high-grade sarcomas with a high rate of metastasis and worse

prognosis. Tumor size (> 4 cm), mitotic rate (> 2 mitosis/10 high-power), and tumor cell pleomorphism are some features that suggest malignant potential.<sup>2,11-14</sup>

Wide local excision is current treatment of choice for breast GCTs, whether they are malignant or not. Surgical margins must be wide and completely free of tumor cells, although it is extremely difficult if the tumor infiltrating into adjacent muscles and other structures. Adjuvant radiation only gives to malignant GCTs with uncertain benefit. Local recurrence has been reported after incomplete excision as late as 10 years after removal, especially when margins are irregular or insufficient.

## CONCLUSION

Breast GCTs remain a diagnostic challenge for radiologists, physicians, surgeons and pathologists. The definite diagnosis is solely relying on the pathological findings. The best way of diagnosis is to perform a preoperative core biopsy, which can help surgeons select the less aggressive procedure instead of mastectomy. There are few reports on breast GCTs with  $\alpha$ -1-antitrypsin positivity, and it may indicate different cell origin(s) or tumor differentiation.

## CONFLICT OF INTEREST

The authors declare that they have no competing interests.

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