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Review Article

Granular Cell Tumor of Breast: Review of Literature

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Abstract

Granular cell tumors (GCTs) are rare benign soft tissue tumors that can occur anywhere in the body, especially in the head and neck. GCTs was considered a myogenic tumor, however, immunohistochemistry (IHC) confirmed that GCTs were soft tissue tumors derived from nerve tissue. Currently, GCT are accepted to be derived from the Schwann cells of the nerve sheath.; they are almost never malignant, but can mimic a carcinoma clinically, radiologically and microscopically. GCTs is usually a slow-growing, painless tumor involving the skin and soft tissues that is mostly located in the head and neck region, especially the tongue. The breast is one of the least common sites involved by GCTs.

The finding of a suspicious lump often entails subsequent diagnostic procedures that can pose significant anxiety on patients before reaching a challenging differential diagnosis. immunohistochemistry showed strongly positive staining of tumors cells with S100 and CD68, confirming the diagnosis of GCTs. The physical and psychological burden is even more significant when such findings occur during the follow up of a previous oncologic condition. Sometimes the fear for a potential local or distant recurrence can be responsible for a misdiagnosis and lead to patient overtreatment.

Keywords: granular cell tumor; breast cancer; pathology; immunohistochemistry

Introduction

Granular cell tumor is a soft tissue neoplasm of neural origin, that can arise anywhere in the body and is particularly rare in the breast. There are only a few reported cases of GCT of the breast (GCTB) in the literature. Granular cell tumors (GCTs) is a rare type of tumor originating from the Schwann cells of peripheral nerves and is usually encountered in the head, neck, and tongue regions [8,9].

In 1931, Abrikossoff identified that, although they were originally noted in the tongue, GCTs were also associated with the breast [1]. GCTs are rare and account for approximately 0.5% of all soft tissue tumors. However, GCTBs are even rarer. They account for 5% to 15% of all GCTs and are mostly benign [2] Up to 8.5% of all GCTs arise in the breast [40] accounting for 0.1% of all cases of breast neoplasms [51]. Taking into account of all GCTs in all the sites, females are affected 2-3 times more commonly than men [13]. GCTs arises from interlobular breast stroma or cutaneous tissue of breast [37-39]. Granular cell tumor of breast (GCTB) is rarely reported as malignant, as having more than three of the following manifestations: the behave of necrosis, the presence of spindle cells, large nuclear body, high level of mitosis, high rate of nuclei/cytoplasm, and pleomorphism [3].

On pathological examination, the cells mostly contain a unusual granular eosinophilic cytoplasm along with classical nuclei and abounding lysosomes, whose cytoplasm is positive for CD68, S100 protein and neuron-specific endolase (NSE) in the immunohistochemical stain [4]. GCTB mainly occurs in females similar to breast malignancies, but has also been reported in the male population, accounting for 6.6% of all GCTB cases [5]. Radiological findings of GCTs can be nonspecific in the breast, and are often indistinguishable from those of breast malignancies. They can be small, round, well-circumscribed masses, but also present as indistinct, stellate, sometimes combined with hypodense rims, spiculated with or without calcifications, and skin thickening, associated with the pectoralis on mammography [6]. T hese tumors on ultrasound are frequently heterogeneous, solid, and poorly defined masses with a posterior shadow and a high depth to width ratio, which often denotes malignancy. Similar to mammography, GCTB on ultrasound has a wide range of properties [7].

Some studies have suggested that the presence of sparse internal hyperechoic foci could be used to differentiate GCTs of the breast from carcinomas, which are usually much more hypoechoic and homogeneous [52-53]. Magnetic resonance imaging (MRI) of the breast is not so effective in diagnosis of GCTs as breast malignant tumor [7] Due to the infiltrative growth pattern of GCTs, it may clinically and mammographically simulate invasive carcinoma [42].

Discussion:

GCTs, often confused with myogenic tumors with a granulosa cell variation [10] Granular cell tumors can be familial. However, studies of their genetic changes are rare [45 Granular cell tumor of the breast is typically a benign neoplasm, although a few cases demonstrating malignant features have been reported in the literature. [11-53]. GCTB can occur in all age groups but is more common in women in their 40s to 60s [12.13]. About 70% of cases of the GCTBs are detected by physical examination (palpation), 26% through screening and 4% during follow-up post breast malignancy [14,15,16].

GCTs present clinically as a hard painless mass that can develop in any part of the breast with the most frequent location is the upper inner quadrant [18-54] and this distribution appear to correspond to the area of innervation of the skin of the breast by the supraclavicular nerve [59]. Clinically, GCT is frequently found in middle aged female. In the breast, it may present as palpable mass less than 3 cm without pain because it grow slowly and stabilize when it is approximately 3 cm in diameter [60].

Metastatic malignant GCTs have been reported in lung, liver, bone and axillary lymph nodes [55].

The probability of local recurrence ranges from 2% to 8% with negative surgical margins and exceeds 20% with positive surgical margins. However, recurrence of benign GCTs does not indicate a poor prognosis, and these tumors generally have a favorable outcome [35]. Histopathological examination with core needle biopsy along with immunohistochemistry is needed to make the diagnosis of GCT. Fine-needle aspiration may not be diagnostic. Microscopy shows sheets or cords of polygonal cells, abundant granular eosinophilic cytoplasm, and bland small round nuclei, without atypia or marked nuclear pleomorphism.

Pathological examination with immunohistochemical staining, particularly for S-100 protein, is crucial for confirming the diagnosis of GCTs [56]. GCTs stain negative for cytokeratin, myoglobin, desmin, neurofilament protein, glial fibrillary acidic protein, and lysozyme. [33,34]. Among the features usually associated with malignancy, only spiculated margins and ring enhancement have been described in GCTs of the breast [19]. GCTs generally do not express estrogen, progesterone, or androgen receptors, which suggests that sex hormones do not directly influence tumor growth unlike other breast malignancies [21,22]. The MRI findings in GCTs of the breast are also nonspecific, and the available image archive is limited. Hence, the features described to date rely on only a few reports, which are far from revealing a widely accepted set of findings. Although no consistent signal intensity has been observed in T1-weighted sequences, such GCTs are said to be isointense or hyperintense in T2-weighted sequences [26-57].

Mammography frequently shows hyperdense to isodense focal asymmetry or an irregular mass with obscured or indistinct margins [23]. A spiculated heterogeneous enhancing mass with persistent kinetics has been reported on MRI [27]. Ultrasound usually reveals a solid mass with posterior shadowing suggestive of carcinoma [30-31]. Sonographically guided biopsy of the lesion is the diagnostic procedure of choice [30-32] Only one study investigated FDG activity in benign granular cell tumors of the breast, which exhibited no significant radiotracer uptake on PET/CT (SUVmax 1.8). [24]. Local recurrence is associated with incomplete excision hence a complete clearance of the tumors with histologically clear margins is paramount. Axillary sampling or sentinel lymph node biopsy is not indicated [41]

GCTs is classified as malignant when it metastasizes to regional lymph nodes or distant sites or otherwise causes death [46].Cytologically, breast GCTs has a varied differential diagnosis including benign lesions like fibrocystic lesion with apocrine metaplasia, fat necrosis, and malignant tumors like ductal carcinoma with apocrine metaplasia [28].Cytologically apocrine cells have a well-defined cytoplasmic border in contrast to the undefined cytoplasmic borders characteristic of GCTs cells. [28] Moreover, the cytoplasmic granularity is more prominent in GCTs [28]. Benign breast lesions have two-dimensional sheets comprised of ductal and myoepithelial cells, in contrast to syncytial or three-dimensional clusters of cells in GCTs [28]. The literature on the staging of GCTs is sparse, and there is currently no standardized staging system specific to GCT [47-48].

Granular cell tumor of the breast is treated by wide excision. Local recurrence may occur after incomplete excision, but sometimes it is difficult to distinguish between recurrence and asynchronous multifocal lesions. Direct invasion of an axillary lymph node by a granular cell tumor of the breast that arose in the axillary tail has been reported [17].

they are considered high-grade sarcomas with high rate metastasis and short survival [29] In the rare instance of malignant granular cell tumors, standard surgical management, including sentinel node biopsy, is recommended, with a limited role for adjuvant therapies such as systemic therapy or radiation therapy [25]. One patient presented with a 4 cm breast tumor and multiple pulmonary metastases that were confirmed histological to be metastatic granular cell tumor [43]. Another patient was found to have axillary metastasis when a tumor initially excised from the upper anterior chest wall recurred in her right breast [44].

However, in the malignant GCTs, the local recurrence rate is up to 41% after surgical excision, and up to 62% of them develop distant metastasis, so long-term follow-up is necessary [49]. Malignant GCTs of the breast are extremely rare, only six cases having been reported in the literature. Given their rarity, most of the literature on GCT of the breast consists of small case-series or case reports [58].

Conclusion

GCTB are rare and can mimic breast cancer. accurate diagnosis via core biopsy and immunohistochemistry is crucial to avoid unnecessary mastectomy or aggressive treatment. The diagnosis can be achieved with a core needle biopsy using the appropriate immunohistochemical panel and should be intensively positive for S-100 and negative for both progesterone and estrogen receptors. According to existing literature, GCTs typically are not responsive to radiotherapy and chemotherapy [50]. Radical local excision with negative margins is recommended in all cases of GCTs, as positive margins are contributed to recurrence of the neoplasm. [20]. These tumors have an extremely favorable prognosis and adjuvant chemotherapy or radiation has not been shown to improve survival [36].

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