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RESEARCH ARTICLE

GRANULAR CELL TUMOR OF THE BREAST - A DIAGNOSIS TO CONSIDER: CASE REPORT AND LITERATURE REVIEW

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Abstract

Granular Cell Tumors (GCTs) or Abrikossoff's tumors are ubiquitous lesions that are currently assumed to arise from perineural Schwan cells. Granular Cell Tumors of the Breast (GCTBs) are rare tumors, representing about 5 to 15 % of all GCTs and 6,7 out of 1000 cases of breast neoplasms. They occur usually in premenopausal African-American women and are by large benign, even though in extremely rare cases they can express malignant behavior or coexist with malignant lesions. GCTBs are of particular significance as they mimic breast malignancies both clinically and radiologically. Histological examination is mandatory for the diagnosis of GCTBs and IHC seems to be the gold standard for this diagnosis, indeed, our tumor cells show strong positivity for the S-100 protein. Wide local excision is the only treatment for GCTBs that are associated with an excellent prognosis. In this article we report a case of GCTB with a brief literature review, the aim of this work is to draw the attention of senologists and pathologists toward this misleading tumor, wich should be routinely recalled as differential diagnosis of breast malignancies in order to avoid over treatement of patients.

Introduction:-

It was Weber, in 1854, who first insinuated the existence of Granular Cell Tumors (GCTs) [1, 2, 3]. Afterwards, this neoplasm was fully described in 1926 by Abrikossoff who also reported the first GCT of the Breast (GCTB) in 1931 [1, 2, 3, 4]. Virtually, GCTs may be encountered in any body site since they arise from perineural Schwann cells of the peripheral nerves [5]. GCTBs, for instance, arise from intralobular breast stroma within the distribution of the cutaneous branches of the supraclavicular nerve [6, 7, 8]. Indeed, strong positivity of tumor cells to S-100 protein and their ultrastructural similarities with Schwan cells, supportthe previous theory and the neural or neuroectodermal origin of GCTs [8, 9]. GCTBs are rare lesions, usually benign, with a particular capacity to mimic breast malignancies clinically, radiologically and macroscopically. Thus, we found interesting to report this case of GCTB,intending to highlight this neoplasm as a differential diagnosis of breast malignancies and to emphasize the importance of immuno-histochemistry (IHC) in the diagnosis of breast masses.

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Case presentation

A 56-year-old female with no significant personal or family history, presented at our department with a slow growing (6 month) left breast mass, discovered during breast self-examination.

The physical examination found a 2 cm nodule in the upper inner quadrant near to the junction of inner quadrants of the left breast. The nodule was painless, poorly defined and mobile. No skin changes or axillary lymphadenopathies were found.

The ultrasonography showed an echoic heterogeneous mass of the upper inner quadrant of the left breast, with poorly defined borders, measuring approximatively 14,5 mm. The ultrasound investigation revealed also a suspicious homolateral lymph node of 7 mm.

On mammography, the nodule was deep, visualized in the junction of inner quadrants, it was round with irregular margins. Therefore, the Breast Imaging Reporting and Data System (BIRADS) category 4 was given.

No abnormal fibro-glandular tissue patterns in other parts of the left breast or in the right breast were observed.

Considering our mass suspicious for malignancy, an ultrasound guided percutaneous biopsy using an automated needle was performed. The histological findings were compatible with a Granular Cell Tumor of the Breast (GCTB) and our patient was subject to wire guided wide local excision (Figure 1) with a post-operative radiological control.

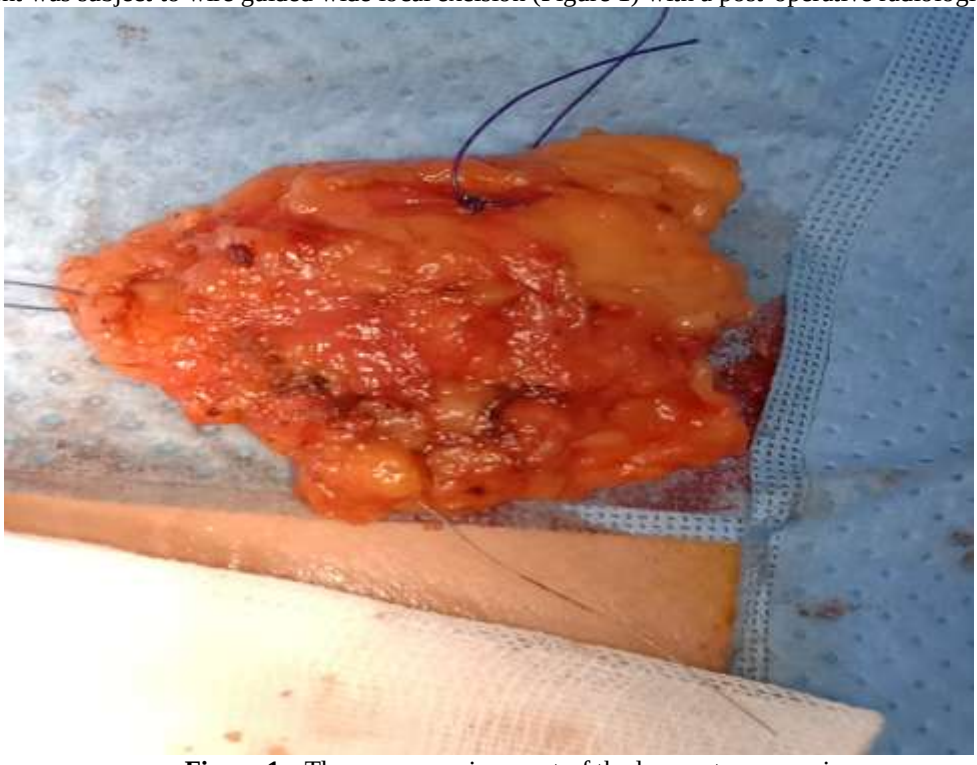

Figure 1:- The macroscopic aspect of the lumpectomy specimen.

The macroscopic examination of the specimen found a 1 x 0,7 cm firm mass. The microscopic examination showed a tumoral proliferation, composed of large cells arranged in sheets and separated by fibrous septa, the cells cytoplasm was particularly abundant with eosinophilic granules that were positive for the Periodic Acid-Schiff (PAS) reaction. No mitosis was observed within the specimen (Figure 2). On immuno-histochemistry (IHC) investigation, the cells were strongly positive for the S-100 protein (Figure 3). The final histopathological report was consistent with a GCTB that was excised completely with free margins.

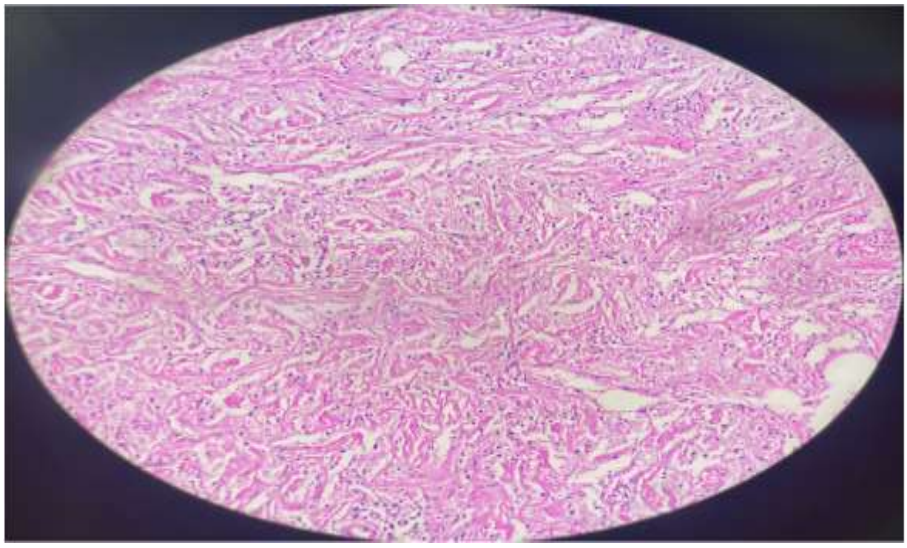

Figure 2:- The microscopic aspect of granular cell tumor of the breast (HES x 200).

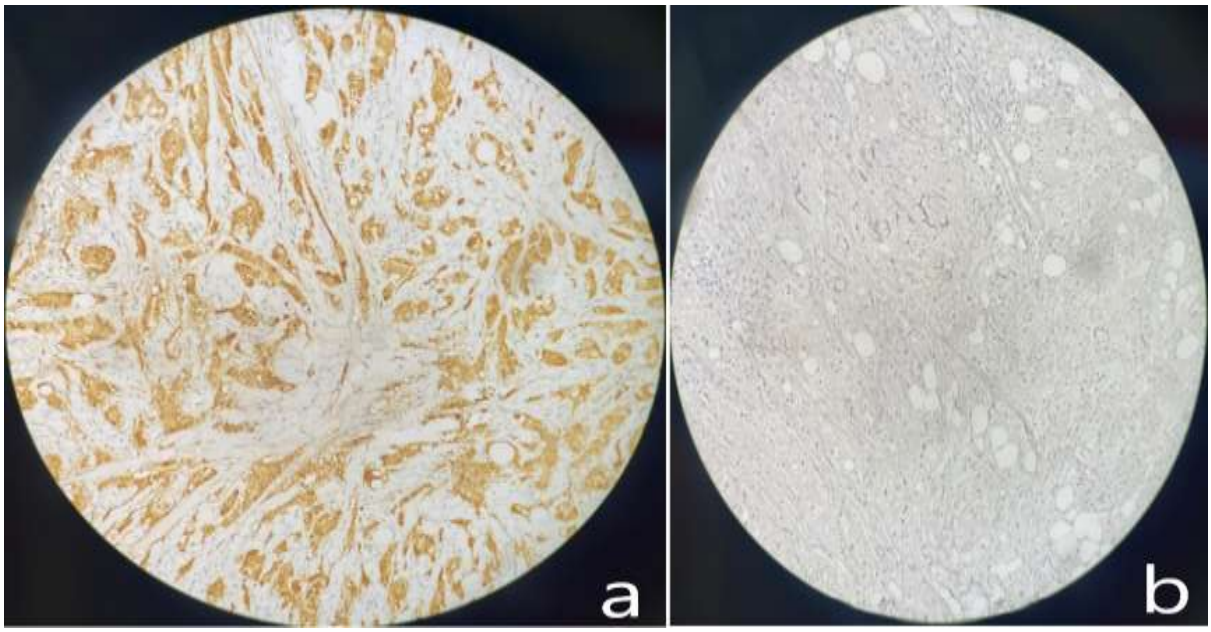

Figure 3:- The immunohistochemistry features of granular cell tumor of the breast.
a : The tumor cells are strongly positive for the S-100 protein
b : The cells are negative for the cytokeratine

For the past year, the patient has been regularly follow-up, both clinically and radiologically, no recurrence is objectified until the date.

Discussion:-

Granular cell tumors (GCTs) of the breast (GCTBs) represent about 5 to 15 % of all GCTs [1]. In spite of being considered as rare breast tumors, GCTBs prevalence, as recent data suggests, reaches 6,7 out of 1000 cases among the clinical population, which makes this affection of higher significance than previously thought [1, 10]. It is interesting to mention that 6,6 % of GCTBs cases were reported in male patients and the ratio of men to women, regarding this neoplasm, is 1/9 [1, 11]. Although in nearly all cases GCTBs behave in a benign fashion, there have been some malignant variation noted in the literature representing 1 to 2 % of cases [1, 12]. GCTBs are commonly described in premenopausal women with a mean age of 40 years and a range between 30 and 50 years [1, 9, 13, 14].

Our patient is 56-year-old which is faintly older as compared to previous statistics. Studies shows also a slight predominance of African-American women in the mater of GCTBs [13].

An analysis of series cases realized in 2009 revealed that 70 % of GCTBs cases were detected, as in our case, by palpation, 26 % through screening and 4 % during follow-up post breast cancer [1]. GCTBs don't seem to present a side preference and can be encountered in any breast part. Nonetheless, as well as breast malignant tumors, they present a predisposition to the upper outer quadrants [1]. Still, within our patient, the tumor was found in the upper inner quadrant – junction of inner quadrants of the left breast.

Clinically, as in our case, the vast majority of GCTBs are solitary, slow growing, painless and firm masses. They can range from well circumscribed to poorly defined tumors. They are usually mobile but can be fixed either to the pectoralis major muscle or to the skin. These tumors can be associated to skin changes (such as thickening, dimpling, tethering and retraction) and rarely to lymphadenopathies, thus mimicking malignancy [1, 15, 16, 17, 18, 19, 20].

Alluding to mimicking malignant tumors, Rosso et al described a special entity of GCTBs that arises in mastectomy scars post removing ductal carcinomas, hence resembling recurrent carcinoma, they named this entity granular cell traumatic neuromas [21].

While the large majority of GCTBs are solitary, multicentricity and coexistence with malignant lesions, especially with ductal carcinoma, has been outlined in roughly 10 % of cases [8, 11, 22].

As we mentioned before, about 1 to 2 % of GCTBs behave in a malignant fashion. Malignant variants of GCTBs are considered high-grade sarcomas with high-rate recurrence, high-rate metastasis and short survival [23, 24]. Metastases from malignant GCTBs have been reported in axillary lymph nodes, lungs, liver and bones [24, 25]. Clinical characteristics of GCTBs that are suggestive of malignancy include rapid growth, large size (> 4 cm) and associated lymphadenopathy [26, 27].

Like other breast masses, GCTs are first investigated employing mammography and ultrasound.

On mammography, GCTBs might take the aspect of a heterogeneous, isodense or hypodense lesion, going from round and well-circumscribed to irregular and spiculated [19, 28] (Figure 4). Microcalcifications are not typical features of GCTBs [2, 28].

On ultrasonography, GCTBs could take the appearance of an irregular, solid lesion with weak internal echo and marked posterior acoustic shadowing [5, 27, 29] (Figure5). Those suspicious sonographic findings are not systematic, GCTBs might be more benign-appearing [5, 27, 29].

Other imaging technics including Magnetic Resonance Imaging (MRI), dynamic magnetic resonance mammography and Positron Emission Tomography with Computed Tomography (PET-CT) could be used while investigating GCTBs. The previous technics are particularly useful to distinguish benign and malignant tumors [1]. However, none of the radiological modalities have yet revealed specific characteristics of GCTBs, the findings are variable and often pointing towards breast malignancies. For our patient, category 4 was given to the tumor under the Breast Imaging Reporting and Data System (BIRADS), which refers to a suspicious abnormality.

Figure 4:- X-Ray of a lumpectomy specimen.

The GCTB appearing as a high density speculated mass [1].

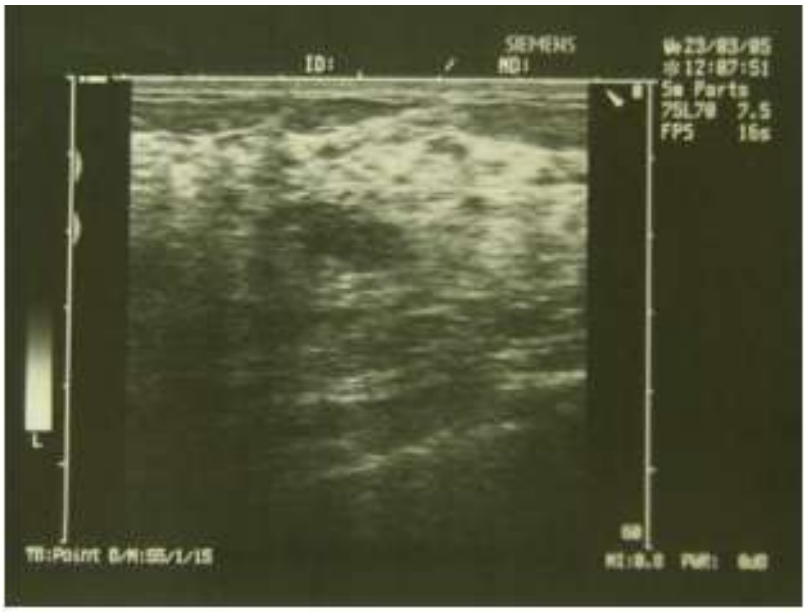

Figure 5:- Ultrasound aspect of a GCTB. The mass is hypoechoic with a posterior shadowing [1].

Given the imprecision of clinical and radiological examinations in diagnosing GCTBs, histological investigation is mandatory for the diagnosis. Ultrasound guided percutaneous biopsy of the breast lesion is for us the procedure of choice for histological sampling. However, many authors consider the Fine Needle Aspiration (FNA) as sufficiently accurate for the diagnosis [1].

Macroscopically, GCTs are greyish-white in color and firm to cut [28, 30]. Microscopically, the tumor is composed of large round or polyhedral cells with round, centrally located nuclei and an abundant granular eosinophilic cytoplasm. The cells of GCTs are arranged in nests and sheets in a variable amount of collagenous stroma [8, 18]. The granular aspect of tumor cells, that shows a positive reaction to Periodic Acid-Schiff (PAS) with Diastase, is mainly related to the accumulation of lysosomes [31]. This granularity makes our tumor easily mimic an apocrine

carcinoma or a metastatic tumor. In another hand the positive PAS reaction is non-specific and may be observed in tumors arising from connective tissues, smooth muscles, endothelial and epithelial cells [32]. Considering the details aforesaid, the immuno-histochemistry (IHC) looks like the gold standard for the definitive diagnosis of GCTs.

On IHC, as in our case, the cells of GCTs show strong positivity for S-100 protein. The tumor cells are also positive for Neuro-Specific Enolase (NSE), CD68 and Vimentin. The cells are negative for all epithelial markers such as Cytokeratin, Epithelial Membrane Antigen and Carcinoembryonic Antigen [18, 26, 31].

A malignant behavior of GCTBs can be suspected if three or more of the following features are found: large size (> 4 cm), rapid growth, local invasion, increased mitotic rate (> 2 mitosis / 10 high-power fields at x 200 magnification) and variation in cells size and shape [6, 26].

Treatment of GCTBs depends on their benign / malignant behavior. Regarding benign GCTBs, the recognized treatment is wide local excision, even though our literature review didn't give more accurate precision concerning the limits [1, 5, 6, 7, 12, 14, 33]. Our patient was subject to wire guided wide local excision since the nodule was small, poorly defined and mobile. Prognosis of benign GCTBs is excellent, recurrence occurs in 2-8 % of cases [34] and further recurrence is likely related to non-radical excision in the first instance [7]. The rare cases of recurrence should be looked into and an annual follow-up must be proposed to patients [2, 5]. Malignant variant of GCTBs should be treated in line with other breast malignancies [7].

Conclusion:-

Even though Granular Cell Tumors of the Breast (GCTBs) are rare and commonly benign, they are of particular significance as they mimic breast malignancies clinically, radiologically and macroscopically. The purpose of this article is to remind practitioners to recall GCTBs ahead of any breast mass and to proceed routinely to immuno-histochemistry (IHC) witch seems to be the gold standard for the diagnosis. In fact, tumor cells show strong positivity to S-100 protein while they are negative for all epithelial markers. Our main take home message is that a misdiagnosis of this misleading lesion can lead to unnecessary radical treatment while a wide local excision is admitted to be sufficient and associated with an excellent prognosis.

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