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Case report

Vulvar granular cell tumor (ABRIKOSSOFF TUMOR); a tumor of vulva which is rare but needs care

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1. Introduction

Granular cell tumor (GCT) is a rare clinical entity derived from Schwann cells of the outer sheath of the peripheral nerves. This benign tumor was first described by Abrikossoff in 1926 as soft nodular tumor of the head and neck about half preferentially located on the tongue (Trojano et al., 2017; Laajili et al., 2017; Sonmez et al., 2016; Pereira and Khan, 2015; Yaghoobi et al., 2015; Crivelin et al., 2014; Hong et al., 2013). The vulvar location is extremely rare being only 10% of the cases (Trojano et al., 2017; Hong et al., 2013).

The age distribution of the tumor may vary between elderly patients to even children (Yaghoobi et al., 2015; Crivelin et al., 2014; Hong et al., 2013). The cases usually accumulates between the fourth and sixth decades of life (Trojano et al., 2017; Sonmez et al., 2016; Pereira and Khan, 2015; Yaghoobi et al., 2015; Crivelin et al., 2014; Hong et al., 2013). There is no remarkable geographic variation and may be seen in every part of the world. GCT is more commonly encountered among blacks (Trojano et al., 2017; Laajili et al., 2017; Pereira and Khan, 2015; Crivelin et al., 2014).

The tumor on vulva usually appears as a mobile solitary nodule located in the subcutaneous tissue. The overlying skin may also show some changes such as thickenning, ulceration or hyperpigmentation (Trojano et al., 2017; Hong et al., 2013). By these features, it may be confused with many benign and malignant pathologies in clinical practice. This slow-growing tumor may sometimes be multicentric and aggresive in behavior (Trojano et al., 2017; Pereira and Khan, 2015; Hong et al., 2013). There is a slight risk of malignancy or malignant transformation at the rate of 2% (Trojano et al., 2017; Laajili et al., 2017). When this occurs, there may be a risk of metastatic disease with the spread to lymph nodes and distant tissues (Trojano et al., 2017).

The recommended treatment of this disease is wide excision of the tumor with free margins (Trojano et al., 2017; Laajili et al., 2017; Sonmez et al., 2016; Pereira and Khan, 2015; Yaghoobi et al., 2015; Crivelin et al., 2014; Hong et al., 2013). It is not easy to achieve this goal because of the vague margins in the subcutaneous tissues (Laajili et al., 2017). If the margins are involved, a re-excision procedure with free margins is usually adviced in benign or malignant lesions (Trojano et al., 2017; Laajili et al., 2017; Sonmez et al., 2016; Pereira and Khan, 2015; Yaghoobi et al., 2015; Crivelin et al., 2014; Hong et al., 2013). No current evidence to support the use of adjuvant therapies such as the local radiation therapy or chemotherapy or the control of the disease in malignant cases with fatal outcome (Laajili et al., 2017; Yaghoobi et al., 2015). In both benign and malignant cases, the patients should be counseled and called for regular follow-up in order to detect recurrences (Trojano et al., 2017; Laajili et al., 2017; Pereira and Khan, 2015; Hong et al., 2013).

In this case report, our aim is to discuss the vague points in the clinical aspects, diagnosis, treatment and follow-up of this unique and rare tumor of the vulva. Even rare, it should be taken into consideration among vulvar solid tumors in differential diagnosis.

2. Case

A 33-year-old female with one child discovered a few milimeters of

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mass on the left labium majus. When the patient applied to a physician at that time, it was evaluated as a folliculitis of the hair adnexa and managed expectantly. In two years following this diagnosis, the mass slowly enlarged up to almost 4 cm. in its diameter. The case sought medical advice for this situation and was scheduled for the excisional treatment under general anesthesia.

The clinical appearance of the lesion was as a solid mass about 4 × 3 × 3 cm in its size. The mass was mobile and the overlying skin was not attached to the lesion. The appearance of the skin covering the mass was the same of the skin of the labium majus. There was no skin change. The mass was deeply seated in the middle of the labium majus. There was no palpable lymph nodes in the both inguinal areas. No other lesion was discovered on other parts of the body as well. The patient had no complaint except the concern about the enlarging mass.

The mass was widely excised up to the appearence of a normal fat pad of the labium and it was removed completely. The hemostasis was secured in the bed of the excision and a penrose drain was placed under the skin before suturing the incision. The postoperative period was completed without any complication. The patient was discharged and was called for follow-up in three months.

The pathology of the lesion was reported as granular cell tumor (Abrikossoff's tumor) by the pathologist. The patient was informed about this pathology and counseled for the crucial role of the follow-up to detect recurrences. There is scanty amount of information in the literature about this tumor and all was based on case reports. The management and follow-up demontrated some debatable areas. It was decided to report this rare case with discussion about these vague points.

On macroscopic examination, the tumoral lesion was 3.5 × 3.0 × 2.2 cm in size with poorly defined border. Cut section of tumor revealed white irregular fibrotic areas in surrounding adipose tissue (Fig. 1). Microscopically, the tumor was composed of sheets of cells or nests separated by thick collagenous bands. Cells were round and polygonal with distinct borders. Cytoplasms contained coarse granules and small dense nuclei. These cells irregularly extended into adjacent adipose tissue and in some areas reached to the surgical margin. Therefore, it is recommended to follow-up with physical examination for the surveillance of the recurrences of this benign lesion of neurogenic in origin.

Granular cell tumor showing cords and nest of tumoral cells with abundant granular eosinophilic cytoplasm and round dense central nucleus.

PAS (Periodic Acid Schiff) staining showed PAS positive large granules in cytoplasms (Fig. 2). Staining with **S-100 protein** revealed diffuse positivity in almost all cells (Fig. 3).

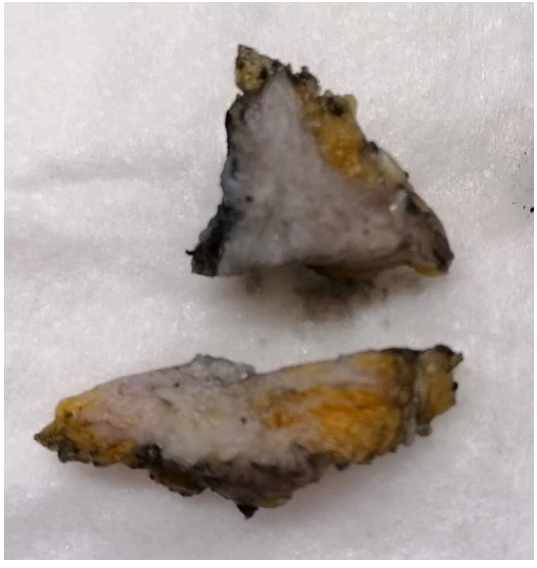

Fig. 1. Macroscopic appearance of the tumor and section cut.

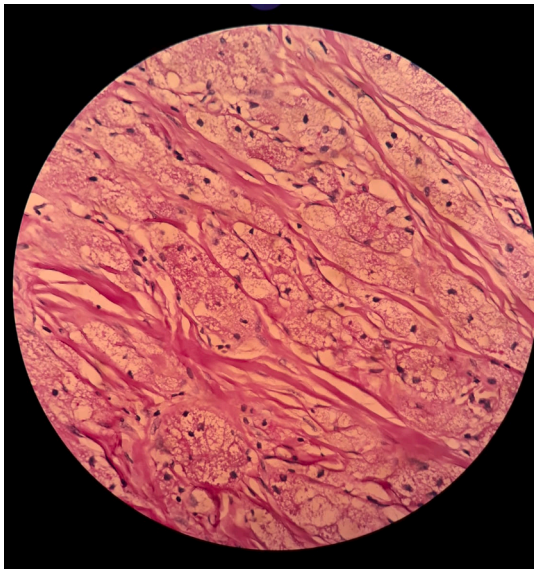

Fig. 2. PAS (Periodic Acid Schiff) staining (PAS positive large granules in cytoplasms).

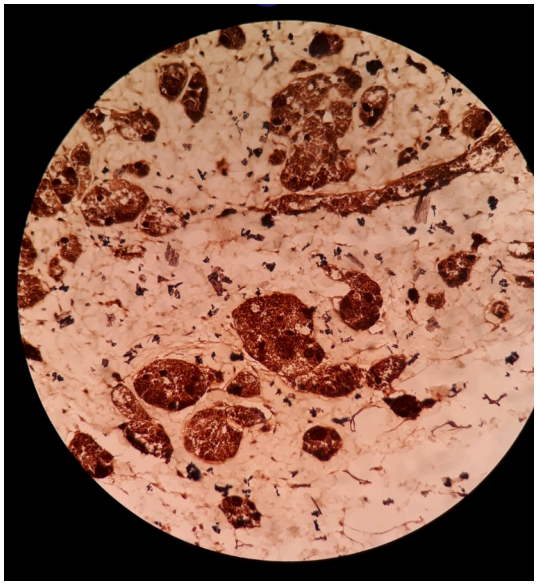

Fig. 3. S-100 immunostaining (Staining with S-100 protein revealed diffuse positivity in almost all cells).

3. Discussion

Granular cell tumor (Abrikossoff's tumor) is a very rare and almost always benign tumor which can occur elsewhere in the body. Until 1999, overall nearly 400 cases has been found in the literature (Yaghoobi et al., 2015).

The tumor usually arises in the skin, subcutaneous and submucosal tissues of the head and neck. The tongue and oral cavity are the most common sites in these regions (Trojano et al., 2017; Laajili et al., 2017; Hong et al., 2013). On the contrary, the less common sites are extremities, genital and visceral organs. The vulvar GCT is even more infrequently encountered phenomenon and only 143 cases could be reported on this site. Uterus, cervix, ovary, vagina and episiotomy scar are the rarest locations mentioned in the literature (Trojano et al., 2017). The vulva is the site of the origin of GCT at rate of 5–16% (Laajili et al., 2017; Sonmez et al., 2016; Hong et al., 2013).

The tumor can be seen in all age groups and even in children (Yaghoobi et al., 2015). In adults, the average age distribution is between 30 and 50 years-old (Crivelin et al., 2014). Our patient is also in this average age group and 33-year-old female. The tumor started as a small, slow-growing, solitary nodule with no pain and itching as always reported. The solitary tumors usually appear as a small nodule ranging from 0.5 to 3 cm (between <1 to 12 cm) in diameter and in only 10% of the cases, the lesions are multicentric in origin. The multicentric lesions are more prevalant among blacks (Sonmez et al., 2016; Crivelin et al., 2014). The labium majus is the most frequent site on the vulva as in our case. The whole body should be taken into the scope of investigation because 25% of the cases may have multifocal lesions. In some rare cases the probability of familial predisposition was suspected based on the multiple benign or malignant events among family members (Trojano et al., 2017; Hong et al., 2013). There was no other family member of our case with the same benign or malignant tumor.

The clinical diagnosis may not be easy all the time because of the similarity of the lesions with some benign and malignant dermatologic pathologic lesions. The nodules may be confused with sebaceous cysts, lipomas, fibromas, hidradenomas, papillomas, Bartholin duct cyst, epidermal cyst, melanoma and the delay in the exact diagnosis with the indication of biopsy is not an exception (Trojano et al., 2017; Pereira and Khan, 2015; Yaghoobi et al., 2015). In our case, the lesion was initially assumed to be a folliculitis and an excision could be performed because of significant interval enlargement after two years of expectant management. Favorably, the rate of malignancy or malignant transformation can be disregarded in accordance with the available current literature and the risk of malignancy in solitary lesions is even less (Trojano et al., 2017; Laajili et al., 2017; Sonmez et al., 2016; Hong et al., 2013). The malignancy is more common in advanced ages (Laajili et al., 2017). The vulvar biopsies should be used liberally in order to avoid malignancy. The lesions may be with ulceration, hyperpigmentation, itching and skin changes of the overlying skin (Crivelin et al., 2014). The overlying skin was normal and there was no skin change in this case.

The histopathologic diagnosis is also difficult needing a differential diagnosis of several pathologies. The common origin of tissue of GCT is dermis or subcutaneous tissue but less frequent locations are submucosa, smooth or striated muscle or internal organs (Sonmez et al., 2016). The tumors of all these tissues should be ruled out for correct diagnosis. Dermatofibroma, skin-appendage tumors, compound melanocytic nevi and seborrheic keratosis should be taken into consideration in microscopic differential diagnosis (Crivelin et al., 2014). The histopathologic characteristics of these lesions are not specific. These poorly circumscribed lesions have pale polygonal cells and abundant eosinophilic cytoplasm (Crivelin et al., 2014). The specific feature of these cells are the granules which they contain in the cytoplasm (so-called **granular cell tumor**). The granules are PAS-positive and diastase-resistant. The cells are round with normochromatic nuclei. The largest intracytoplasmic eosinophilic granules are called **pustulo-ovoid bodies of Milan** (Crivelin et al., 2014). Microscopically, the differential diagnosis may not be easy with granular cell variants of basal cell carcinoma, melanoma, leiomyoma, leiomyosarcoma, angiosarcoma, fibrous histiocytoma, oligodendriglioma, malignant glioma and ameloblastoma due to these characteristics (Yaghoobi et al., 2015; Hong et al., 2013). Because the overlying epidermis may demonstrate acanthosis and high mitotic rate (Crivelin et al., 2014). Pseudoepitheliomatous hyperplasia of the overlying stratified epithelium is a common skin lesion and may be misdiagnosed as squamous cell carcinoma (Sonmez et al., 2016; Hong et al., 2013). The routine microscopy is insufficient tool for the diagnosis and needs further procedures. In addition to these conventional techniques, electrone microscopy may also be useful as reported by Gokaslan et al. (1994).

The immunohistochemistry is an important adjunct for diagnosis. In GCT, the cell contain many lysosomes and the granules show positive staining with PAS. S-100 protein, neuron-specific enolase, laminin and CD-68 are the other stains which the cells are immunoreactive (Sonmez et al., 2016). The granular cells are immunohistochemically positive for S-100 protein, vimentin and neuron-specific enolase, 98%, 100% and 98%, respectively (Hong et al., 2013). In our case, the granules of the cells of the tumor show positive staining with PAS as well as resistant granules with dPAS. Besides, S-100 and vimentine were also positive. On the contrary, there was no staining with SMA and CD-34. These findings confirmed the immunohistochemical diagnosis of granular cell tumor.

There is always a risk of malignancy in GCT at the rate of 2% (Hong et al., 2013; Trojano et al., 2017; Laajili et al., 2017; Sonmez et al., 2016). The vulvar GCT should be differentiated from malignant tumors if it is ulcerated (Laajili et al., 2017). The clinical characteristics suggesting malignancy are rapid tumor growth, advanced age, the diameter of the tumor >4 cm, vascular invasion, necrosis, and local recurrence with poor prognosis (Pereira and Khan, 2015). None of these features was present in the presented case but there was not enough time passed for the evaluation of recurrence. The criteria of malignancy was first proposed by **Fanburg-Smith** under six items in 1998. According to that, the cases are classified as benign, atypical and malignant. Necrosis, vesicular nuclei with nucleoli, increased mitotic activity (>2 mitosis/10 high power fields to 200× magnification), high nuclear to cytoplasm ratio and pleomorphism are considered malignancy characteristics. The finding of only pleomorphism is the indication of benignity (Trojano et al., 2017; Laajili et al., 2017; Sonmez et al., 2016; Pereira and Khan, 2015; Yaghoobi et al., 2015; Crivelin et al., 2014). No evidence of malignancy were detected in this case.

The recommended treatment in these tumors is wide local excision of the tumor (Trojano et al., 2017; Laajili et al., 2017; Sonmez et al., 2016; Pereira and Khan, 2015; Yaghoobi et al., 2015; Crivelin et al., 2014; Hong et al., 2013). The surgical margins should be wide enough in order to guarantee the clear margins. Because of the poorly defined borders of the tumor, this goal may not be achieved in all cases. The risk of recurrence 2–8% if the the margins are negative in benign cases. Otherwise, this risk increases up to 20% with involved margins (Laajili et al., 2017; Pereira and Khan, 2015). Mohr repeat sectioning with horizontal frozen section tissue mapping was proposed by some to ensure the negative margins during surgery (Pereira and Khan, 2015). Even if it is rare, the recurrence can occur after simple excision of the lesion. Exceptionally, the malignant transformation of the benign lesion can even be seen in the literature (Yaghoobi et al., 2015).

Whether benign or malignant, the straightforward approach is the re-excision or wider local excision (Trojano et al., 2017; Laajili et al., 2017; Pereira and Khan, 2015; Yaghoobi et al., 2015; Hong et al., 2013). The concept of re-excision of the lesions with positive margins does not stand on solid evidence rather than being a reflex behavior. Because there is no study we could find in the literature comparing the re-excision immediately after first surgery with positive margins or re-excision after recurrence. It is not clearly known if the outcome of the patient is negatively affected when the excision is performed after recurrence. On the contrary Rose et al. (2009) stated that the resection margins or depth of the tumor was not in relationship with malignancy or recurrence in case series of musculoskeletal system GCT (Hong et al., 2013; Rose et al., 2009). In one review, one of the study (Papalas et al., 2010) supports this reality since two of 7 patients with positive margins underwent re-excision after 14 and 8 years with negative margins and with stable outcome. In our patient, surgical margins are involved and the straightforward reaction is re-excision in this situation. The decision should be made according to the benefits of the patients. With re-excision, at least 80% of the patients will have unnecessary surgery with 2–8% risk of recurrence even in negative margins (Laajili et al., 2017; Pereira and Khan, 2015). Furthermore, there is no evidence of adverse outcome if the excision is performed after recurrence in benign cases. In this way most of the patients which will not recur at all probably would be saved from evident complications of surgery.

Besides, the defect with more radical re-excision will result in a poor cosmetic appearance. Especially in some patients, the cosmetic issues in the genital organs are very important with adverse psychologic effects.

In the presented case with only solitary nodule, it is not justifiable to do re-excision under these circumstances. Trojano et al. (2017) in their literature review reported that some patients have not accepted second surgery or re-excision with no recurrence in benign cases of their follow-up (Trojano et al., 2017). Without solid evidence in this issue we recommended expectant management until recurrence for our patient and the patient was called for close follow-up in three months.

Evidently, there is no study comparing expectant management vs. re-excision due to the rarity of the disease. The decision must be based on the follow-up outcomes of the published cases in the literature. In some of the reported cases, the re-excision was recommended but the patients refused (Rivlin et al., 2013; Sonmez et al., 2016; Levavi et al., 2006). No recurrences were detected after 18 months and 7 months respectively and the diameters of the tumors were less than 4 cm (Trojano et al., 2017; Sonmez et al., 2016). The poor prognosis is associated with the tumor size >4 cm. In one of the cases with positive margins of Hong et al. (2013), the follow-up lasted 97 months with no recurrence (Hong et al., 2013). In our opinion, some patients as this case having solitary benign tumors <4 cm in size with involved margins may be followed-up until recurrence without re-excision.

4. Conclusion

GCT is a very rare tumor especially in vulvar localization with mostly benign in nature. It should be taken into consideration among differential diagnosis of vulvar benign and malignant tumors. Immunohistochemistry is the most useful tool for the exact diagnosis. The whole body should be target of investigation to rule out any benign or multifocal lesions. The malignant cases are at the rate of 2% and should be managed accordingly. The primary approach is the surgical complete resection with clear margins. In cases with involved margins, a re-excision is always recommended to prevent recurrences which may occur even in benign cases. In scarcity of solid evidence in the current literature, we recommend follow-up instead of re-excision especially in some patients with benign solitary tumors <4 cm in size until recurrence before performing second surgery. We believe this will be more respectful for the cosmetic concerns of the patients with positive psychologic effects.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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