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CASE REPORT

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Granular cell tumor of the vulva: six new cases

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Abstract Granular cell tumors are rare neoplastic skin and soft tissue lesions: only 1–2% are malignant. Five to sixteen percent occur in the vulva. We present our experience with granular cell tumors of the vulva in six patients, all of whom had wide local excisions and were followed-up in our outpatient clinic for 3–171 months. One died of an unrelated cause. None of the others has evidence of the disease.

Keywords Granular cell tumor · Vulva

Introduction

Granular cell tumors are rare neoplastic skin and soft tissue lesions. They are generally benign, solitary, small nodules palpable on the skin surface. Only about 1–2% of these tumors are reported as malignant [31, 19].

Granular cell tumors have been described in the vulva, cervix, and ovary [9, 27]. Although rare, the most common occur on the vulvar area accounting for 5–16% of all such tumors [7, 8, 10].

We present our 15 years of experience with six cases of granular cell tumors of the vulva managed in the Division of Gynecologic Oncology, at the Rabin Medical Center.

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Patients and methods

Six patients with granular cell tumors of the vulva were identified by review of the computerized pathology records and outpatient files from 1990 to 2004. At referral, patients had a thorough history taken and physical and gynecological examinations, followed by diagnostic biopsy under local anesthesia. Treatment consisted of wide local excision under spinal or general anesthesia. Follow-up was conducted at the clinic.

One of the authors (D.B.) revised all pathological slides and confirmed the original diagnosis.

Results

The patient characteristics are shown in Table 1. Their age ranged from 44 to 72 years (average 58.8 years). Presentations included a palpable nodule, an enlarging lesion, or a pruritus, of several months' duration. In two patients, the lesion was found incidentally on routine gynecological examination. One had recurrent multisite lesions, and is described in detail in the "Case report." Two patients had margin involvement after primary surgery. Repeated excision 3 months later revealed a squamous papilloma in one case. The other patient refused re-excision.

Follow-up ranged from 3 to 171 months (average 149 months) and consisted of detailed clinical and imaging evaluation at each visit. None of the patients had evidence of disease. One patient died of cardiac causes 78 months after tumor removal.

Table 1 Characteristics of six patients with granular cell tumor of the vulva

Patient	Age	Site and size	Presentation	Outcome	Remarks
1.	61	Rt. major labium 12 mm×6 mm×3 mm	Pruritus	Margins involved	Further excision at 3 months—squamous papilloma
2.	47	Rt. major labium 15 mm×10 mm×10 mm	Routine gynecological examination	Clear margins	
3.	61	Lt. major labium 12 mm×10 mm×7 mm	Palpated growth	Clear margins	
4.	72	Lt. major labium 20 mm×15 mm×10 mm	Enlarging mass	Margins involved (refused further excision)	
5.	68	Rt. major labium 20 mm×20 mm×10 mm	Routine gynecological examination	Clear margins	Died—cardiac causes (74 years)
6.	44	1. Rt. Finger 2. Rt. Groin 3. Multicentric vulva + Rt. toe	Enlarging mass	Clear margins	Multicentric, metachronous, and synchronous

Case report

This 57-year-old woman, married with two children, was admitted in 2004 for treatment of granular cell tumors of the vulva and right toe. She had a 13-year history of granular cell tumors in the right hand and right groin. The latter tumor stained positive for S-100 after surgery, but repeated wide excision revealed no residual tumor. On current admission, 2.5 years later, the patient presented with an enlarging growth in the left perineal area. Biopsy revealed incomplete excision of a granular cell tumor. Chest X-ray, vaginal ultrasonography, and abdominal computerized tomography were negative. We detected a slightly elevated lesion measuring 30 mm×15 mm×15 mm in the left perineal area and 40 mm×15 mm×15 mm lesion in the right perineal area, extending to the fourchette (Fig. 1). A third 10 mm×10 mm×5 mm tumor was palpated in the right labium minus. In addition, a 10 mm×7 mm×5 mm subcutaneous lesion was found on the right toe (Fig. 2).

Under spinal anesthesia, the foot lesion was excised, followed by wide local excision of the vulvar lesions. Frozen section study of the right perineal lesion showed clear margins.

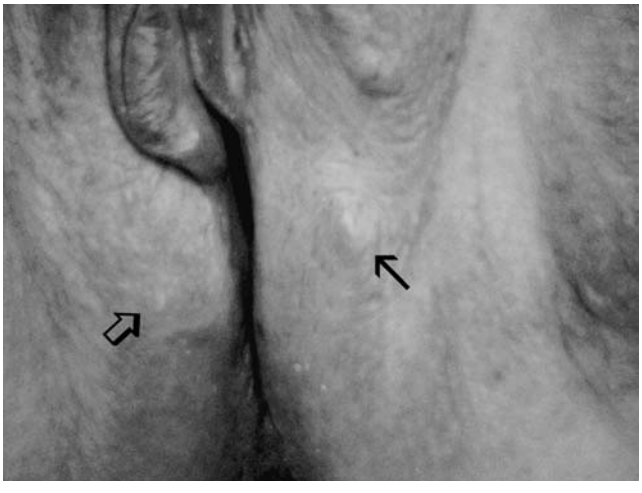

Fig. 1 Patient 6. Vulvar granular cell tumor. Note slightly elevated left perineal lesion (*thin arrow*) and a right perineal lesion extending to the fourchette area (*wide arrow*)

The histological report revealed complete excision of the perineal tumors. A few tumor cells were noted in the labium minus tumor, reaching the deep surgical margin, and residual granular cell tumor was found in the toe, reaching the surgical incision in one area. There was no cellular atypia. All tumors stained positive for the S-100 protein. Immunostaining for Ki-67 was positive in less than 1% of cells.

Discussion

Granular cell tumors are usually solitary, subcutaneous, or soft tissue lesions of various sizes [17] appearing most frequently on the head, neck, and tongue, but they are also described anywhere on the body [24]. Clinical presentation is usually of firm nodules, but they can also appear as cysts, papules, or verrucose lesions [16].

They occur more often in Africo-American women [28]. Some rare familial involvements have been reported [19, 30].

Weber, in 1854, was the first to describe a granular cell tumor, and Abrikossoff, in 1926, reviewed five new cases and designated the name granular cell myoblastoma, alluding to its origin, considered then to be of smooth muscle [2, 34].

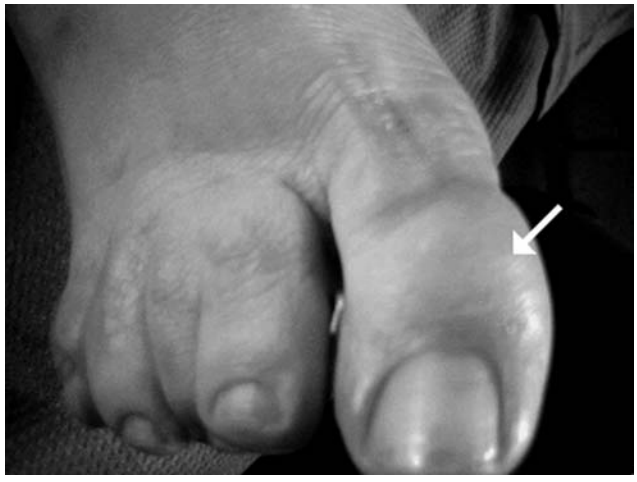

Fig. 2 Patient 6. Granular cell tumor of the toe (*arrow*)

A variety of cell types have been implicated in the histogenesis of GCT, smooth muscle cells [23], fibroblasts, and histiocytes [1, 5, 20, 26]. However, these rare tumors appear to arise from neural tissue resembling Schwann cell derivation, suggested by electron microscopy [12], and later proven by immunohistochemical presence of the S-100 protein [22].

Since many of these tumors are asymptomatic, they are frequently diagnosed as an incidental finding during an examination or at the time of an unrelated procedure [4, 15, 17]. Some present as pain, pruritus, or an enlarging mass [17].

Microscopically, granular cell tumors display oval, or polygonal cells arranged in nests separated by bands of dense fibrous tissue. In some tumors, the borders are not sharply defined. Groups of cells may extend from the main tumor, appearing as "infiltrating" segments. Other tumors appear with confluent growth with well-demarcated "pushing" borders [3].

The cells have small nuclei with abundant eosinophilic and coarse cytoplasm, containing periodic acid—Schiff-positive, diastase-negative, resistant granules [14]. These nuclei rarely contain mitotic figures [7].

In cases with immediate subcutaneous lesions, the epidermis overlying the area of the tumor frequently shows a degree of pseudoepitheliomatous hyperplasia, characteristic of the irritant effect of the tumor. This erroneously might be diagnosed as well-differentiated squamous cell carcinoma [35].

Before planning treatment, clinicians should take a detailed history and do physical and other examinations (chest X-ray, vaginal and abdominal sonography) to exclude multicentric lesions. For benign tumors, management consists of local excision with wide margins. Frozen section is optional. Some authors advocate Mohs procedure—repeat sectioning with fresh horizontal frozen-tissue mapping, until clear margins are achieved [13, 32].

Malignancy is rare (1–2% of cases) [11, 18, 19, 31, 33]. Several fatalities have been reported, occurring mainly with metastases in the lung and brain [17, 21].

The potentially malignant behavior of these tumors is often ignored, and is realized only after local recurrence or distant metastases occur [18, 31], even when the primary granular cell tumors showed no histologic features of malignancy [17, 24].

In an attempt to define clinical features associated with increased malignant potential, Jardines et al. [18] suggested increased tumor size (< 4–5 cm), advanced age at diagnosis, and local recurrence to be significant prognostic markers.

Tsuchida et al. [33] in comparing 35 malignant with 110 benign granular cell tumors found that the average sizes of the tumors were 8.1 and 1.2 cm, respectively. The average age was 48 years in the malignant and 32 years in the benign groups. Malignant cases were found more commonly in females (F/M ratio: 2.9/1); whereas in the benign group, the ratio was 1/1.8.

Tsuchida et al. [33] also found atypical mitosis to be of significant predictive value for malignant behavior. However, they claimed that distinction between benign and malignant cases might be histologically difficult.

Fanburg-Smith et al. [11] in reviewing a large series of granular cell tumors in their institution, classified them as malignant if three or more of the following histologic criteria were met: increased mitotic activity (> two mitoses/ten high-power fields at 200× magnification), presence of tumor necrosis, large nucleoli, prominent spindling, high nuclear:cytoplasmic ratio, and pleomorphism [11].

Feulgen DNA histomorphometry demonstrated aneuploidy in a patient with apparent lung metastases, whereas tumors from patients with a benign course as well as from a patient with multisite involvement were diploid [21].

Immunohistologic criteria were also evaluated by Fanburg-Smith et al. [11]. They reported that p53 immunostains were negative in all benign granular cell tumors, while p53 expression was seen in greater than 10% of the cell population in 21 of 25 (79%) malignant tumors.

Ki-67 was also found in less than 1% of the benign cases, while 14 of 25 (56%) malignant tumors had Ki-67 immunopositivity in up to 30% of the cell population [11].

In malignant granular cell tumors, histological margins should be carefully evaluated and repeated surgery, if required, should be performed promptly, with regional lympadenectomy. Postoperative radiotherapy should be considered in cases where complete excision cannot be achieved [29]. However, the effectiveness of radiotherapy or chemotherapy has not yet been established [18, 19, 29].

The vulva accounts for 5–16% of all granular cell tumors [7, 8, 10]. Vulvar lesions appear, usually, on the labia majora, but other sites as perianal, perineal, and clitoral have also been reported [17, 25]. Approximately, 70 vulvar cases have been reported to date, only six were malignant [29]. The malignant potential of the tumor demands close follow-up and prompt biopsies of all new lesions.

All our patients had wide local excisions with a long follow-up (average 149 months). One died of unrelated causes and the other five are disease-free.

Three to sixteen percent of granular cell tumors are multiple and synchronous [15, 17, 19, 20].

One of our patients had multifocal granular cell tumors, some appearing metachronously, some synchronously, over 13 years. All were benign (no atypia; Ki-67 positivity—less than 1%). Margin involvement was found in one vulvar lesion. We did not operate immediately because microscopic foci of granular cell tumors have been shown to regress when margin involvement is small [20]. The toe involvement in our patient is also very rare. Granular cell tumors of the foot accounted for 0.07% of a series of 2,720 foot lesions [6]. An English-language literature review [32], found only 18 cases with

foot or toe involvement, and added one patient with a plantar lesion.

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