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DERMATOFIBROSARCOMA PROTUBERANS WITH UNUSUAL PRESENTATION IN VULVA

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Abstract Gynecological sarcomas are rare and their location in the vulva and vagina has an incidence of 5% of all malignant neoplasms in the female genital tract. We present the case of a 54-year-old patient with a diagnosis of dermatofibrosarcoma protuberans in the vulva, an infrequent pathology with less than 60 cases reported worldwide in this anatomical location. Clinically, it is locally aggressive, due to the proliferation of spindle cells with pleomorphism and frequent mitotic figures infiltrating the reticular dermis and subcutaneous cellular tissue, giving rise to variable size tumors with high local recurrence rates. The first-line treatment is surgical excision of the tumor with Mohs micrographic surgery among other surgical techniques for complete circumferential peripheral and deep margin assessment. However, identification of carcinogenesis mechanisms where the chromosomal translocation t (17; 22) (q22; q13) is recognized, forming the COL1A1-PDGFB fusion gene, which participates in stimulating tumor cell proliferation, allowing treatment with tyrosine kinase inhibitors such as imatinib for neoadjuvant therapy of surgically unresectable tumors and local recurrences.

Key words: cancer, dermatofibrosarcoma, vulva, platelet-derived growth factor b, collagen type 1 alpha 1 chain

Resumen ***Dermatofibrosarcoma protuberans con presentación inusual en vulva.*** Los sarcomas ginecológicos son infrecuentes y la localización de estos en vulva y vagina tienen una incidencia del 5% de todas las neoplasias malignas del tracto genital femenino. Presentamos una paciente de 54 años con diagnóstico de dermatofibrosarcoma protuberans en vulva, el cual es una patología infrecuente con menos de 60 casos reportados a nivel mundial en esta localización anatómica. Clínicamente tiene un comportamiento localmente agresivo, debido a la proliferación de células fusiformes con pleomorfismo y frecuentes figuras de mitosis que infiltran la dermis reticular y tejido celular subcutáneo, dando origen a lesiones tumorales de tamaño variable y con altas tasas de recurrencia local. El tratamiento en primera elección es la escisión quirúrgica del tumor con técnicas como cirugía micrográfica de Mohs u otras técnicas quirúrgicas para evaluación completa del margen periférico circunferencial y profundo. Sin embargo, la identificación de mecanismos de carcinogénesis donde se reconoce la translocación cromosómica t (17; 22) (q22; q13), formando al gen de fusión COL1A1-PDGFB el cual participa estimulando la proliferación celular tumoral, ha permitido la utilización de los inhibidores de la tirosina quinasa como el imatinib para la realización de terapia neoadyuvante en casos de tumores irresecables quirúrgicamente y en recurrencias locales.

Palabras clave: cáncer, dermatofibrosarcoma, vulva, factor de crecimiento beta derivado de plaquetas, cadena alfa1 de colágeno tipo 1

Vulvar cancer accounts for about 0.4% of all cancers, with preference for older-aged women in the seventh decade of life[1]. The most common histological type is the squamous cell carcinoma, diagnosed in 90% of cases, followed by melanomas, extramammary Paget's disease, adenocarcinomas, basocelular carcinoma, sarcomas and undifferentiated carcinomas[1, 2].

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Primary gynecological sarcomas are infrequent and account for 3 to 4% of all the malignant neoplasm of the female genital tract, with anatomical distribution as follows: uterus 85% of the cases, ovary 8%, vulva and vagina 5%, and the remaining 2% in other gynecologic organs, being leiomyosarcoma the most frequently seen histological type, followed by endometrial stromal sarcoma[3].

The scientific literature has reported fewer than 60 cases of dermatofibrosarcoma protuberans (DFSP) with an extremely rare location in the area of the vulva[4-6], according to the new WHO classification of soft tissue tumors, it belongs to the category of fibroblastic/ myofibroblastic tumors with differentiation of intermediate biological potential[7], being locally aggressive, marked

tendency for local recurrence and extremely infrequent distant metastases[2,6,8].

Clinical case

A 54-years-old woman with a lesion in labia majora, progressive growth, painless, and firm on palpation, accompanied by slight hyperpigmentation of the surrounding skin. On physical examination no suspicious adenomegalies were identified in the inguinal region. The gynecological examination was otherwise normal. Non-contrast and contrast-enhancing MRI were obtained reporting an expansive growth tumor in the vulva, solid in appearance and infiltrating the subcutaneous tissue. The oncologic gynecology department decided to surgically excise the lesion with circumferential peripheral and deep margins.

The macroscopic histopathology report describes it as a tumor which largest diameter measures 12 cm, partially covered by light brown skin with irregular edges and firm consistency (Fig. 1). The microscopic examination shows a proliferation of spindle cells with hyperchromatic nuclei, organized in a storiform pattern with frequent mitotic figures (7 mitoses per 10 high-power fields), infiltrating from the reticular dermis to the subcutaneous cellular tissue. No tumor necrosis was identified, nor lymphovascular or perineural invasion. Margins were lesion free. The immunohistochemistry exhibited strong positivity of the tumor cells for CD34 and Vimentin, and no reactivity for AML, S100, Factor XIIIA and Desmin: The cell proliferation index measured with KI-67 was 60% (Fig. 2). With these findings the diagnosis of Dermatofibrosarcoma

Fig. 1.– Light brown tumor partially covered with skin, and with irregular edges

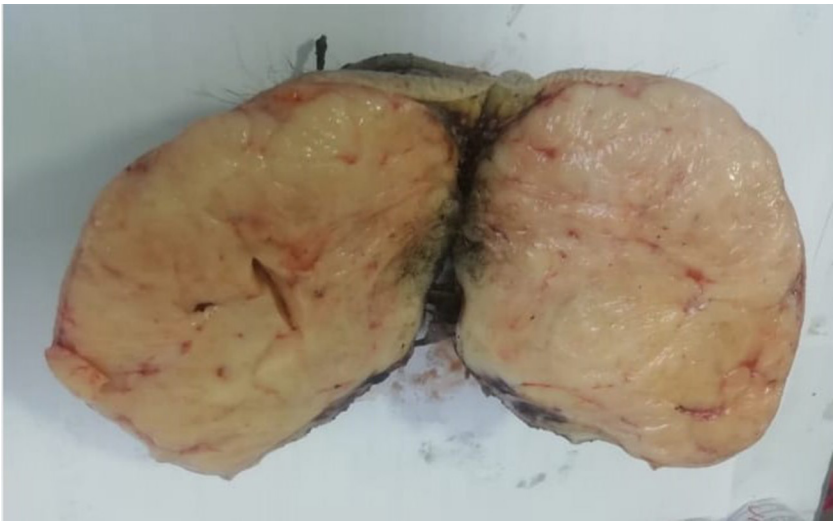
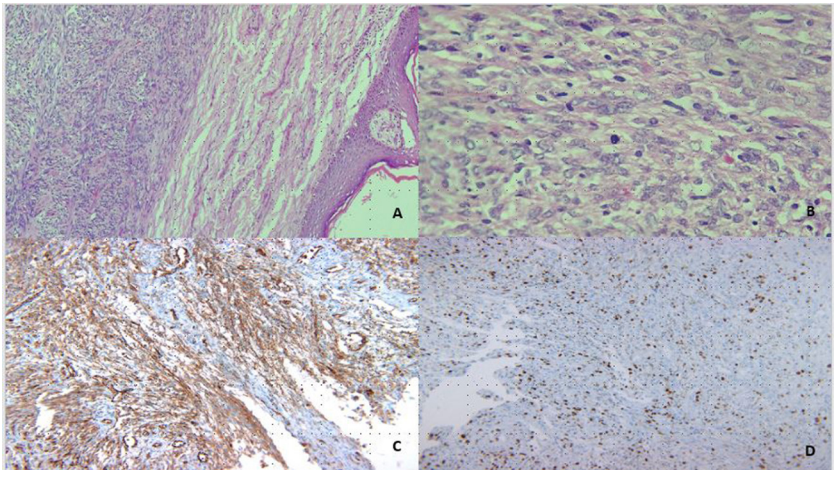


Fig. 2.– A and B: Hematoxylin and eosin (H&E) staining, 10x and 40x. A tumor is found in the reticular dermis, pleomorphic spindle cells with frequent atypical mitotic figures in a storiform pattern. C: Strong and diffuse immunohistochemistry marking of tumor cells for CD34. D: 60% cell proliferation index measured with KI-67



Protuberans was established. Since the peripheral and deep margins were not involved, the patient continued under strict monitoring, not requiring other surgeries and/or drugs. Patient had a local recurrence at 6 months from the diagnosis, with a new 5 cm tumor in the previous scar area, which required the complete excision of the lesion with broad surgical margins. Therefore, molecular cytogenetic studies were carried out in biopsy, finding the chromosomal translocation t (17; 22) (q22; q13) with the COL1A1-PDGFB fusion gene, which motivates the initiation of neoadjuvant therapy with imatinib, to perform tumor cytoreduction, showing as response the decrease of 1.5 cm in diameter. Subsequently, the complete excision of the lesion was carried out with surgical margins of 2.2 cm and 1.5 cm towards the circumferential and deep lateral edges. The patient is currently progressing satisfactorily without evidence of new local recurrences and without metastatic lesions.

Written informed consent was obtained from the patient for the publication of this case report and its accompanying images.

Discussion

Dermatofibrosarcoma protuberans is a rare skin mesenchymal fibrohistiocytic lineage neoplasia which arises in the dermis and hypodermis and accounts for 1% of all soft tissue sarcomas[9]. The most frequent locations are the trunk, proximal extremities and in lower proportions the head and neck[2, 9], with equal distribution in men and women towards the fourth decade of life[6].

The finding of such a tumor in the vulva is very unusual and only series of reported cases are found in the international scientific literature[2, 5, 6, 8, 10-12], with the pathology prevailing in young adult females (fourth or fifth decade of life), clinically described as a firm and nodular mass, growing slowly, asymptomatic, painless, with an average largest diameter of 4.2 cm [4] and located predominantly in the labia majora, followed by the mons pubis and the area adjacent to the clitoris[2, 4-6, 8, 10-12]. In the current case, the patient showed the initial large lip lesion and local recurrence on the surgical scar, following the 6 months after the first intervention, denoting clinically aggressive biological behavior. Among the differential diagnoses included in the clinical analysis are the following: abscess, Bartholin gland cysts, sebaceous cyst and other soft tissue neoplasms[2].

Histologically, it is represented by neoplastic spindle cells arranged in storiform or honeycomb patterns, diffusely infiltrating the dermis, subcutaneous adipose tissue and on many occasions even the adjacent muscle tissue, as observed in the histopathological study of the case show, where the positivity of the strong and cytoplasmic immunohistochemical markers for CD34, with a high mitotic index measured with KI-67 and negativity for AML, Factor XIIA, HMB45, STAT-6 and S100, support a diagnosis of dermatofibrosarcoma protuberans, this immunophenotype being commonly reported in the scientific literature as characteristic of this tumor lesion, together with the expression of other markers such as PDGFR-a, PDGFR-b and c-Abl[2, 6]. This immunoprofile allowed to rule out the diagnostic possibilities from the histological point of view, such as neurofibroma, cellular dermatofibroma, malignant tumor of the peripheral nerve sheath, Schwannoma, desmoplastic melanoma, myxoid liposarcoma, leiomyosarcomas and solitary fibrous tumor[2, 6].

In the vast majority of classical dermatofibrosarcoma protuberans cases and its variants the recognized carcinogenesis mechanism is the presence of chromosomal translocation t (17; 22) (q22; q13), resulting in a ring chromosome from the fusion of the gen collagen type I alpha 1 chain and platelet-derived growth factor B-chain gene (COL1A1-PDGFB), which encodes a chimeric protein structurally indistinguishable from subunit β of the platelet-derived growth factor (PDGF), which receptors are expressed in the DFSP tumor cells, and capable of stimulating cell proliferation through autocrine mechanisms[2,4,9] .

Recently, in case series the presence of alternative rearrangements in dermatofibrosarcomas protuberans without PDGFB fusions, in which the fusion Collagen Type VI Alpha 3 Chain - Platelet Derived Growth Factor D (COL6A3-PDGFD)[13] was more frequently identified in chromosomal position 2q37.3 – 11q22.3, evidencing genomic imbalance in the breakpoints and some numerical alterations with additional copies, which mainly through PDGFD, stimulates cell proliferation and angiogenesis[14]. Another fusion recognized in association with PDGFD is elastin microfibril interface-located protein 2- Platelet Derived Growth Factor D (EMILIN2-PDGFD)[13], whose chromosomal location is 18p11.32–11q22.3 and is associated with homozygous deletion of CDKN2A, whose biological behavior reveals fibrosarcomatous transformation and tumor growth in the hypodermis with no connection to the dermis[14].

The recommended treatment for DFSP in the vulva according to the National Comprehensive Cancer Network Guidelines is surgical excision with Mohs micrographic surgery or other surgical techniques for Complete circumferential peripheral and deep margin assessment (CCPDMA)[15], with a strict post-op follow up. However, in surgically unresectable tumors neoadjuvant therapy is considered with imatinib, a tyrosine kinase inhibitor that blocks the cell cycle progress, in a context where cytogenetics (conventional or molecular) allows to identify the translocation t (17; 22) (q22; q13) [15]. On patients with margin involvement, surgical extension is recommended and in local recurrences and metastasis, adjuvant radiotherapy is indicated with 50-60 Gy, or the use of imatinib[2, 6, 15].

In this case, it was decided to performed neoadjuvant imatinib therapy, a tyrosine kinase inhibitor that blocks the advancement of the cell cycle[15], because the t (17; 22) (q22) translocation was identified through molecular cytogenetic studies in the tumor; q13), with the aim of reducing the tumor size and carrying out its complete resection, preserving the largest healthy tissue and thus allowing the anatomical functions of the patient to be

preserved, following the recommendations provided in the NCCN treatment guidelines[15]. Next, surgical excision was performed, repairing and orienting the specimen, thereby allowing a complete evaluation of the deep and circumferential peripheral margins, the patient progressing satisfactorily after the second intervention.

By way of conclusion, dermatofibrosarcoma protuberans in the vulva is an infrequent pathological condition affecting the adult female population locally devastating and with a tendency to local recurrence, therefore, it requires a multidisciplinary approach for proper diagnosis. It requires a multidisciplinary approach to identify the right diagnosis and indicate individualized treatment, through highly effective surgical techniques and recognizing alterations in genetic checkpoints that can offer therapeutic options with less side effects when they are unresectable, recurrent or metastatic.

Conflicts of interest: None to declare

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