CASE REPORT

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Primary vulvar Merkel cell carcinoma

Carcinoma primario de células de Merkel vulvar

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ABSTRACT

Merkel cells were originally described in the stratum basale of the epidermis with neuroendocrine properties. Merkel cell carcinoma of the vulva is an extremely rare and highly aggressive neoplasm. There are few cases of these tumors, most of which have been considered neuroendocrine tumors. The histologic origin and etiology of this disease are controversial. It is known for his aggressive behavior and propensity for early diffusion. Because of its rarity in this location, it is unclear whether it behaves differently from similar skin carcinomas in other locations. A case of primary vulvar Merkel cell carcinoma is presented. Excisional biopsy examination revealed a 4 x 3-centimeter tumor in the posterior third of the left labium majus of the vulva without lymph node involvement. The patient underwent radical vulvectomy and bilateral inguinal lymph node dissection. Postoperative histological evaluation showed no regional or distant metastases.

Key words: Vulva, Carcinoma, Merkel cell, Vulvar neoplasms

RESUMEN

Las células de Merkel se describieron originalmente en el estrato basal de la epidermis, con propiedades neuroendocrinas. El carcinoma de células de Merkel de la vulva es una neoplasia extremadamente rara y altamente agresiva. Existen pocos casos de estos tumores, la mayoría de los cuales han sido considerados tumores neuroendocrinos. El origen histológico y la etiología de esta enfermedad son controvertidas. Debido a su rareza en esta localización, no está claro si se comporta de manera diferente a los carcinomas de piel similares en otras localizaciones. Se presenta un caso de carcinoma primario de células de Merkel vulvar. El examen de biopsia por escisión reveló una tumoración de 4 x 3 centímetros en el tercio posterior del labio mayor izquierdo de la vulva sin afectación de los ganglios linfáticos. La paciente fue sometida a vulvectomía radical y disección bilateral de ganglios linfáticos inguinales. La evaluación histológica postoperatoria no mostró metástasis regionales ni distantes.

Palabras clave. Vulva, Carcinoma de células de Merkel; Neoplasias de la vulva

Introduction

Merkel cells are components of the basal layer of the epidermis and follicular epithelium. They form clusters in areas of sensory perception, close to primary nerve endings. Primary cutaneous Merkel cell carcinoma (MCC) is probably epidermal in origin and is predominantly seen on the head, neck, extremities, and trunk[1]. Primary vulvar MCC is an extremely rare condition, with fewer than 20 reported cases. It has an aggressive behavior and can, in some cases, mimic the clinical presentation of Bartholin's gland abscess[2,3]. A case of primary vulvar Merkel cell carcinoma is presented.

Case report

The patient was 60 years old, gestation 7, para 7, who consulted for presenting vulvar pain and pruritus of approximately 4 months of evolution, which increased in the last month, symptomatology that was previously treated on an outpatient basis with antibiotics, antifungal and topical steroids, without improvement. She reported natural menopause 12 years ago, receiving no hormonal treatment. She denied vaginal bleeding or discharge and personal history of chronic diseases or neoplasms. Cervical cytology results for 9 months were normal.

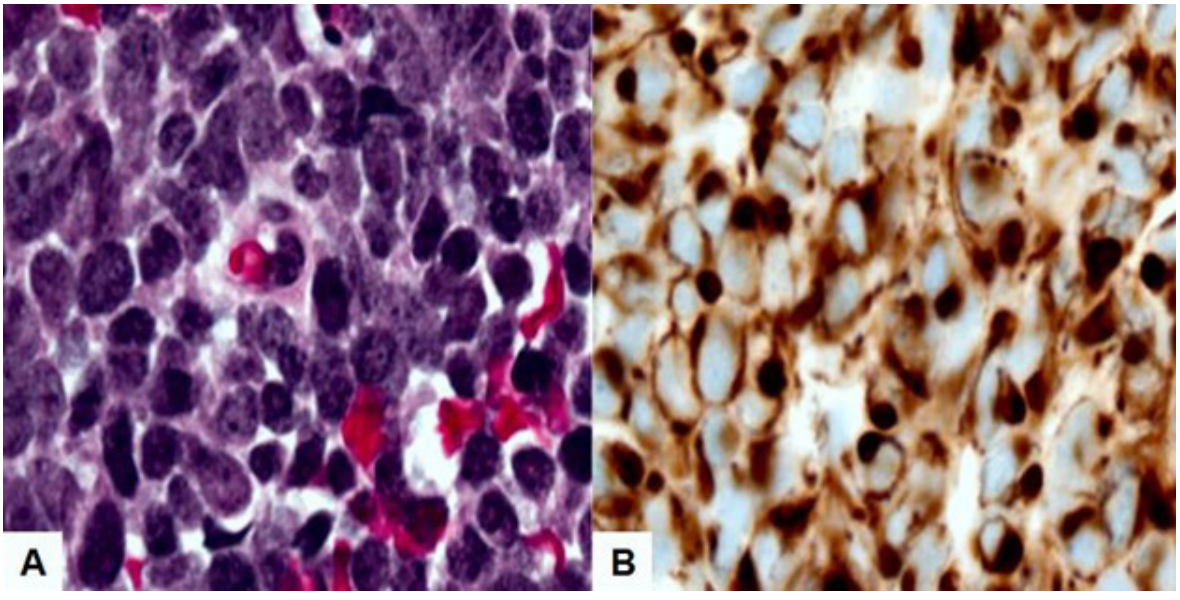
The general physical examination found no alterations in organs and systems. On gynecological examination, a reddish, exophytic, firm, non-ulcerated, mobile lesion of approximately 4 x 3 centimeters was observed in the posterior third of the left labium majus of the vulva, which extended 2 centimeters towards the ipsilateral vaginal wall, without the presence of bloody or purulent discharge. On palpation, both the uterus and adnexa were normal, but bilateral inguinal lymphadenopathy of hard consistency was perceived. Bartholin's glands were normal. No lymphadenopathy was palpated in other areas. Speculoscopy of the cervix and vagina showed no alterations.

Based on the physical examination findings, the patient was scheduled for excisional biopsy due to the possibility of benign tumor, finding a 41 x 35 millimeters tumor, well circumscribed. Microscopically it was composed of small round tumor cells, with scarce eosinophilic cytoplasm, round-oval nuclei with scarce granular chromatin, fine nucleoli grouped in cords, nests and islands. Overlying stratified squamous epithelium was observed. The margins of the biopsy-approximately 21 millimeters from the excised edge to the area closest to the tumor-were not taken up by the lesion. Mitosis and necrosis were observed. Immunohistochemical staining of the tumor cells were all positive for cytokeratin 20, chromogranin A, Cam 5.2 and low molecular weight cytokeratin (Figure 1). Cytokeratin 20 staining had a perinuclear dot pattern characteristic of Merkel cell carcinoma. Immunostaining of the cells was negative for cytokeratin 7, S100, thyroid transcription factor, and desmin. Histologic findings and immunohistochemical staining were consistent with small cell variant vulvar MCC.

The patient underwent radical vulvectomy with bilateral superficial and deep inguinal lymph node dissection (18 in total) to ensure that there was no neoplastic lymph node involvement; no gross tumor was identified. The iliac nodes were not dissected, because the freeze biopsy showed that the deep inguinal nodes did not show signs of malignancy. The patient's postoperative course was uneventful, and she was discharged after 5 days. The anatomopathological evaluation of the surgical specimen showed that the resection margins were free of lesions. Bilateral superficial and deep inguinal lymph nodes were negative for metastatic disease.

Postoperative follow-up, including abdominopelvic ultrasound, chest X-ray and thoraco-abdominal CT scan, showed no evidence of regional lymph node involvement or distant metastases. Laboratory tests were normal, including normal CA-125 and carcinoembryonic antigen values. The patient was referred to the oncology department where she was treated with postoperative radiotherapy of the pelvis, vulva, perineum, and inguinal region according to protocol. During 24

Figure 1. Photomicrograph of small cell variant of vulvar Merkel cell carcinoma. Small cells with large nuclei and scant cytoplasm are seen. A. Hematoxylin-eosin staining. 100X. B. Immunostaining with cytokeratin 20. 100x.



months of follow-up, the patient has remained healthy, with no evidence of recurrence, regional involvement, or distant metastasis.

Discussion

MCC is the only vulvar neuroendocrine tumor of epithelial origin in the literature to date[1]. Initially it was considered to develop from Merkel cells. However, its origin from a stem cell capable of differentiating into different cell lines is now favored. It affects older white adults (97%) 69 to 75 years[4]. It is more common in areas exposed to the sun, such as head, neck, extremities, and trunk, but it can also occur in salivary glands, esophagus or genitals. They are malignant tumors with aggressive behavior and a high rate of local recurrence, metastasis to regional and distant lymph nodes[5].

The possible etiology of MCC is debated. Advanced age, immunosuppression and European ancestry are high risk factors, while ultraviolet radiation contributes to its development[6]. Polyoma virus DNA was detected in tissue samples in more than half of the cases, suggesting a possible oncogenic role[7]. Due to its rarity, it is unknown whether it behaves differently from other anatomical locations[3].

The diagnosis of vulvar MCC is generally late and at the time of diagnosis 48% of patients have metastases in regional lymph nodes and 15% have distant metastases[8]. The usual clinical presentation is a firm, purple-red nodular tumor, without ulceration of the overlying skin. Histopathological analysis of the lesion is required for definitive diagnosis. Tests to rule out disseminated disease include liver function tests, abdominal ultrasound and computed tomography of the thorax, abdomen, pelvis and spine[4], since *postmortem* studies have shown the presence of metastasis to pelvic lymph nodes, liver and vertebrae[8]. Due to the proximity of Bartholin's gland to the vulvar skin, primary neuroendocrine carcinoma of the gland should be considered as a differential diagnosis[2].

MCCs are subdivided into three histologically recognizable groups. The intermediate cell variety constitutes most cases and shows large, solid nodules with diffuse sheets of basophilic cells, characteristic round-oval nuclei, and inconspicuous nucleoli. The second group is the small cell variant which has small round cells with scant cytoplasm, hyperchromatic oval nuclei, and prominent nucleoli. The tumor cells form solid sheets or clusters. The third group is the trabecular variant which is the least common and has round-polygonal cells with abundant cytoplasm, centrally located round vesicular nuclei and discrete nucleoli arranged as nodules, trabeculae, or ribbons[9].

MCCs are difficult to differentiate from melanomas, lymphomas, and metastatic oat cell carcinomas by light microscopy alone, requiring additional diagnostic techniques such as immunohistochemical staining. MCC expresses several molecular markers that distinguish it from small cell carcinoma of the lung and other internal organs[6]. However, both tumors show neurosecretory granules and have an aggressive clinical course. MCC tumor cells stain positively for markers such as chromogranin, synaptophysin, neuron-specific enolase or CD56. Perinuclear staining for cytokeratin 20 is the hallmark that distinguishes these malignancies, as more than 90% are cytokeratin 20 positive, making it the characteristic marker[8]. Another useful antigen marker is thyroid transcription factor, which is positive in 90% of neuroendocrine carcinomas of the lung, 34% of the vagina and 20% of the cervix, but not in MCC[10].

Due to its aggressive behavior, MCC has an extremely poor prognosis. In addition to the stage of the disease, other factors that influence prognosis are tumor size, depth of invasion, histologic differentiation, and lymph node involvement[6]. Multimodality treatment is the ideal practice for this pathology and surgery is the first step of treatment in patients with resectable lesions. Tumor resection with wide margins (greater than 3 centimeters) including the fascia is recommended[4]. Groin dissection is determined by tumor size and freeze biopsy results[11]. Most studies support sentinel lymph node biopsy in cases with clinically normal inguinal nodes, as it can predict the likelihood of nodal involvement, short-term risk of regional involvement and distant spread[12].

All surgical procedures must be accompanied by adjuvant regional radiotherapy, because it increases the disease-free interval compared to surgery alone[13,14]. The use of adjuvant chemotherapy continues to be debated and is generally

reserved for local recurrences or disseminated disease[11]. The combination of cyclophosphamide, doxorubicin and vincristine has an overall response rate of 75% in these cases[14,15].

MCC usually produces early local recurrences that occur in 86% of stage I tumors and in 20% of stage II tumors[5]. Vulvar MCC appears to have more aggressive behavior and worse prognosis than in other locations. Overall mortality exceeds 50% in the two years following diagnosis and the reported 5-year survival is 14%[3].

In conclusion, MCC of the skin is a rare pathologic entity and its occurrence in the vulvar region is extremely rare. It behaves extremely aggressively, producing local recurrences and early metastatic disease. Surgical treatment is the primary treatment modality and adjuvant radiotherapy may be considered. However, tumor recurrence and progression are common problems.

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