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CASE REPORT

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AN UNCOMMON CASE OF VULVAR CANCER METASTATIC TO BREAST

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Vulvar carcinoma corresponds to the fourth gynecological malignancy in incidence, with more than forty thousand new cases being estimated worldwide in 2020. It is a disease characterized by locoregional spread presenting high recurrence rates although distant metastases are an uncommon event. The purpose of this work is to describe the diagnosis, treatment, and clinical course of vulvar carcinoma in a patient who presented regional recurrences and late metastasis to the mammary gland. Vulvar cancer is a disease with a well-defined natural history; but with the advancement of therapeutic possibilities in recent years, it has been possible to improve the prognosis, reducing the chance of locoregional recurrence. Thus, the possibility of distance recurrence must be remembered in inpatient follow-up with locally advanced vulvar carcinoma, even if atypically, as in the case reported.
***Key Words*: vulvar neoplasms, squamous cell carcinoma, breast cancer, local neoplasm recurrence, metastasis.**

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The vulvar carcinoma is an uncommon malignant neoplastic disease compared to the group of neoplasms prevalent in females. It occupies the fourth position for incidence among the most prevalent gynecological cancers and comprises around 5% of female genital tract cancers. Among the histological subtypes of this neoplasia, more than 90% are squamous cell carcinoma, followed by melanoma and basal cell carcinoma [1, 2].

Two hypotheses of carcinogenesis have been described in cases of vulvar squamous cell carcinoma (VCC): one related to human papillomavirus and another resulting from the evolution of chronic inflammatory skin diseases in the vulvar region, such as sclerous lichen [3]. Risk factors such as smoking, multiple sexual partners, common warts, and metabolic syndrome can contribute to the two forms of pathophysiology [4].

VCC has a natural history of locoregional involvement, which, depending on the size of the primary lesion, may have metastases in regional inguinofemoral and/or pelvic lymph nodes. Despite the treatment available, locoregional recurrence rates range from 12% to 37% [5]. Distant metastases are rare, and when they do occur, they usually compromise organs such as the lungs, pleura, and liver [6]. Metastasis to the mammary gland, and sequentially to axillary lymph nodes, is a rare evolution with few documented cases [7, 8]. For patients with stages I and II VCC, there is a 90% five-year survival rate. However, in the presence of locoregional metastases, average survival increases to 40% [9].

The purpose of this report is to describe the diagnosis, the treatment, and the clinical evolution of a VCC in a patient, who presented metastases in the mammary gland, after 10 years of oncological follow-up. This report is part of the research project entitled "Clinical Case Reports in Oncology"; and was approved by the Research Ethics Committee of the Universidade Federal da Fronteira Sul — UFFS (CAAE 31359820.2.0000.5564).

CASE PRESENTATION

A 74-year-old white caucasian female patient is referred for surgical treatment of a VCC diagnosed by a recent incisional biopsy. The primary vulvar lesion was a poorly defined erythematous plaque, 2 cm in diameter and with a small central ulcerated area on a small left vulvar labium, without the involvement of the clitoris. She had palpable lymph nodes ± 1 cm in diameter, hardened, mobile, and delimited in both inguinal regions. Staging exams were carried out that did not show signs of impairment of the disease at a distance. She was then submitted to a modified radical vulvectomy (left hemivulvectomy with preservation of the clitoris) with resection margins of 1.5 cm from the visible lesion including deep tissues down to the deep perineal fascia followed by bilateral inguinal lymphadenectomy. Both surgical procedures were performed with an interval of 20 days. The pathological stage of the disease was defined as pT1bpN2bM0 — IIIB. Thus, adjuvant treatment was proposed concomitant with chemotherapy (cisplatin) and radiotherapy of the vulvar region and inguinal and pelvic lymph node chains (55.80 Gy/31 fractions). In the seventh year of oncological follow-up, a recurrence in the skin of the left vulvar area was diagnosed. She then underwent a new surgical resection and the anatomopathological examination described a squamous cell carcinoma of 2.4 cm in diameter with negative resection margins. The patient was not submitted to adjuvant treatment. Two years later, that is, in the ninth year of follow-up, she was diagnosed with a new VCC recurrence, now on the left vaginal wall. Magnetic resonance imaging of the pelvis described a neoplastic lesion in the vaginal wall involving the rectal wall and the lower region of the bladder. In the other staging exams, no distant metastatic lesions were found. The patient was then submitted to a monobloc resection of pelvic organs (pelvic exenteration including vagina, bladder, urethra, rectum, uterus, and appendages),

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Abbreviations used: VCC – vulvar squamous cell carcinoma.

with the reconstruction of urethral and intestinal transit at the same surgical time. Histopathological examination of the surgical specimen described a moderately differentiated carcinoma, infiltrating the vulvar and vaginal walls, circumferentially, from the uterine cervix to the isthmus and the anterior rectal wall to the chorion — sparing the uterine body, also verified in macroscopic examination (Fig. 1). The patient remained asymptomatic for twelve more months (tenth year of follow-up), she returned with a complaint of a nodule in the right breast. Upon physical examination, a mass was observed at the junction of the lateral quadrants of the breast, measuring ± 3.5 cm, with associated inflammatory signs and imprecise limits, which presented, in the central region, a fistulous orifice through which necrotic material would exude (Fig. 2). It was possible to observe a dense, rounded, partially delimited lesion on the mammography. From the core biopsy of the lesion, and in the histology, it was possible to characterize a moderately differentiated squamous cell carcinoma (Fig. 3). According to the previous clinical history, it was considered to be a distant recurrence of VCC. The patient underwent quadrantectomy with ipsilateral axillary lymphadenectomy and reconstruction with a lateral thoracic flap. The anatomopathological examination of the breast lesion confirmed the diagnosis of the previous biopsy, where the lesion showed invasion into the underlying muscle tissue and the resection margins were free of the neoplasm. Four of the fourteen isolated axillary lymph nodes had metastases, but with no invasion of perinodal soft tissues. Two months after the procedure, new lesions were observed in the thoracic wall, in addition to metastases to both lungs. The patient deceased in 6 months without a response to the systemic treatment employed.

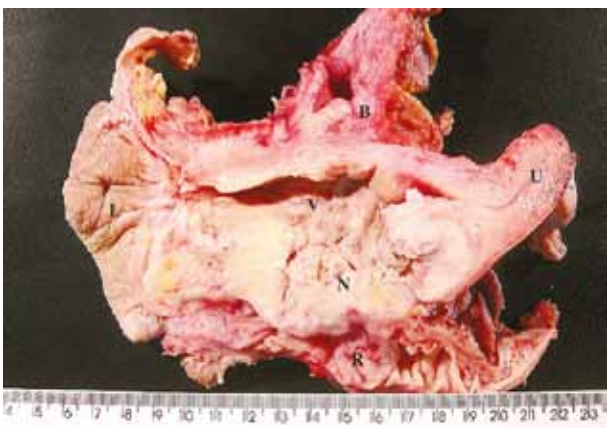

Fig. 1. Macroscopy — longitudinal section of the surgical specimen, product of the pelvic exenteration. L — small and large straight lips; B — bladder; V — vaginal cavity; N — recurrence of the neoplasm; R — straight; U — uterus

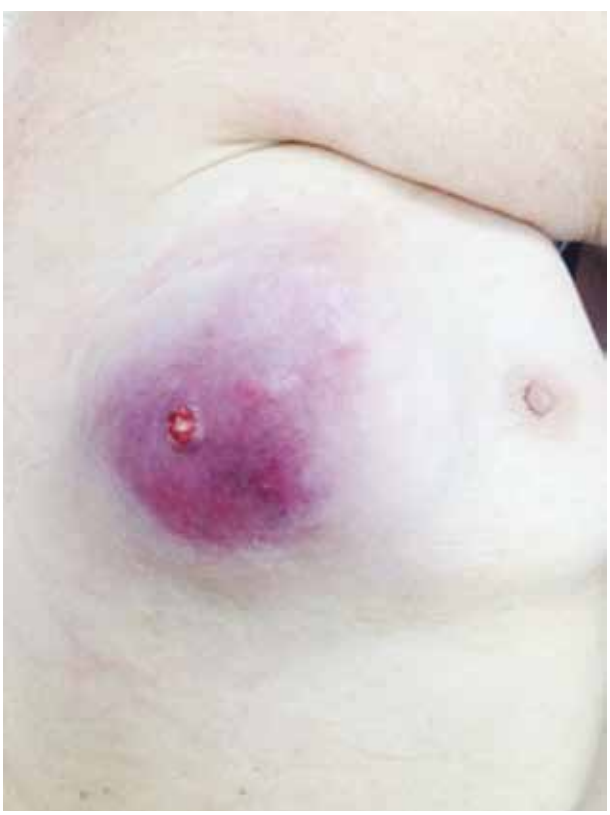

Fig. 2. Clinical aspect of carcinoma metastasis from the vulva to the right mammary gland

DISCUSSION

Vulvar cancer corresponds to 4% of gynecological neoplasms worldwide, with 65% of the cases occurring in developed countries [9]. Tobacco exposure, multiple partners, venereal warts, and a history of cervical cytology with cervical intraepithelial neoplasms lead to a predisposition of increased risk of VCC [10]. The prevalence of human papillomavirus associated with VCC varies from 10 to 70% in different studies [3, 4,

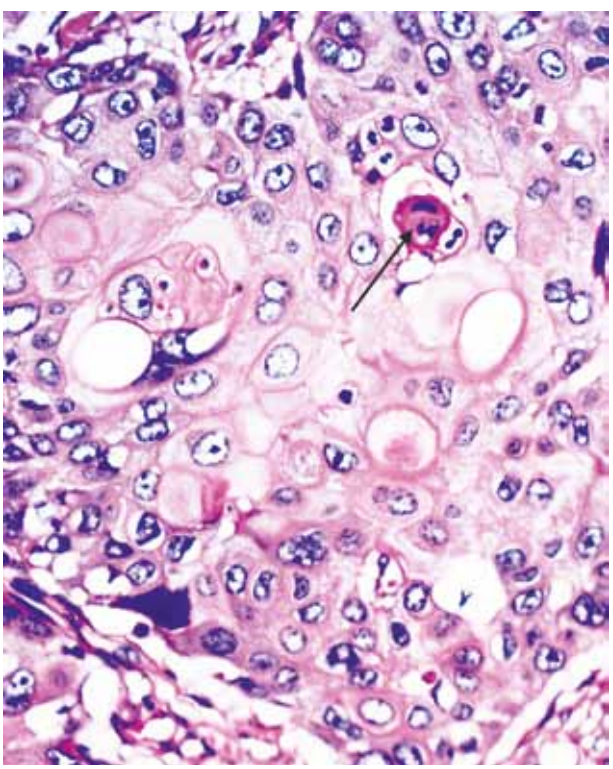

Fig. 3. Histological aspect of breast metastasis from moderately differentiated squamous cell carcinoma (H&E, × 400). Neoplasm is formed by epithelioid cells, rounded, with ample eosinophilic and homogeneous cytoplasm and round/ovoid nuclei, with increased nucleus/cytoplasm ratio. The figures of typical and atypical (arrow) mitoses are present

9]. Clinically, most patients have an erythematous plaque skin lesion, badly delimited, with or without associated ulceration; or a nodular or warty unifocal tumor mass. They usually originate in the region of the labia major, followed by the area of the labia minora, the perineum, and the clitoris [3]. The primary lesion can be multifocal in up to 5% of cases, and synchronously there may be palpable ipsilateral regional lymph nodes due to metastatic neoplasia. The diagnosis is determined by anatomopathological analysis and any suspected vulvar lesion will require biopsy [4, 5].

Most patients present with localized disease (60%), that is, without metastatic involvement (regional or distant), followed by patients with lymph node involvement (30%) or at a distance (10%). The primary VCC lesion in the reported patient was classified as IIIB; that is, the neoplasia had a lesion with a 2 cm extension but had more than two lymph nodes with macrometastases [8, 9]. Patients with VCC of up to 2 cm in diameter and up to 1 mm of stromal invasion do not require lymph node resection. They can be treated only with local resection of the lesion, considering free margins of at least 1.5 cm [10]. For carriers of lesions larger than 2 cm and who do not have suspicious lymph nodes for metastatic impairment (physical examination and imaging tests), sentinel lymph node biopsy may be chosen. It is a technique that can be performed at the same surgical time as the treatment of the primary vulvar lesion [10, 11].

Block resections of the vulvar tumor concomitantly with the complete bilateral inguinofemoral lymphadenectomy has been an increasingly less used strategy, due to high morbidity. Currently, excision of the vulvar tumor and lymphadenectomy through incision is recommended and at different surgical times [12], thus avoiding complications with recurrent seromas, infection, suture dehiscence, or lower limb lymphedema [11, 12]. In the case described, although submitted to resection with wide margins, the patient presented two loco-regional recurrences, probably related to a focus of multifocal neoplasia. In both situations, it was possible to perform resection of recurrences with free margins (R0) [12, 13]. The patient did not indicate a sentinel lymph node biopsy for she presented suspicious lymph nodes of neoplastic impairment upon physical examination. Complete bilateral inguinal lymphadenectomy was performed 20 days after excision of the primary lesion, which may have contributed to no associated postoperative complications.

Distant VCC metastases are rare events, occurring in 8% to 12% of patients. The liver and the lungs are the most frequent sites of metastatic VCC involvement, and the average time for the appearance of distant metastasis is 13.4 months of follow-up. Most patients (around 60%) have one or more local recurrences before spreading from a distance [14]. This chronology of events was also observed in the reported case, in which there were two episodes of local recurrences before the manifestation of metastasis to the mammary gland.

Metastases to the mammary gland are also uncommon, representing 0.5% to 2% of malignant lesions of the breast, being the ones, most often exhibiting breast metastases include melanomas, lymphomas, ovarian cancer, lung tumors, neuroendocrine, and sarcomas [15–18]. Unlike primary carcinomas, breast metastases, in most cases, do not have spiculated margins, skin, or nipple retraction due to the absence of a desmoplastic reaction [19, 20]. On the mammography, skin thickening, irregular opacities, and oval radiopaque lesions with irregular margins are observed. Architectural deformities or microcalcifications are uncommon [21]. Primary breast squamous cell carcinoma is also a rare event. To define that it is primarily in the breast, the predominant type of cell must be squamous cell (more than 90% of the neoplastic area), that the lesion has no relation to the overlying skin, and that there is no evidence of primary carcinoma localization in other anatomical sites [22]. In the reported case, after diagnostic confirmation by histology, it was necessary to know whether it was a primary or metastatic neoplasm in the breast. Due to the previous history of VCC with the same histopathological characteristics, it was considered to be a distant metastasis of vulvar neoplasia.

Despite recent advances in treatment, VCC in advanced stages (lymphatic involvement, local recurrences, and distant metastases) has a poor prognosis. In the United States, the median survival for patients with VCC in five years is 71%. However, these figures vary according to the stage of the disease. For the local disease, the median 5-year life extension is 86%, dropping to 53% with lymphatic involvement. Overall, the five-year survival rate for recurrent VCC is 25% to 50% compared to 50% to 90% for patients with no history of recurrence [18, 23]. The prognosis is influenced by the location of the recurrence and the time interval between the initial diagnosis and the recurrent disease. Studies show a five-year survival after diagnosis of recurrence of 53%, when it is local and early (< 24 months after primary treatment), compared to 76% for patients with late local recurrence (> 24 months after primary treatment). Patients with distant recurrent VCC have five-year survival rates arriving at only 10% [23, 24].

Conclusion. VCC is a disease with a well-defined natural history characterized as a locoregional aggressive behavior malignant disease, which compromises the quality of life and can result in the patient's death. The distant manifestation of the disease is an uncommon event and usually occurs within the first years of follow-up. The patient reported here presented recurrences, both locoregional and distance, in a late manner. The fact of having been control of pelvic disease resulted in a greater time of disease-free survival. Thus, the possibility of distance recurrence must be remembered in the oncological follow-

up of patients with locally advanced VCC, even after the usual five years of cancer follow-up. One should also consider the patient's complete clinical radiological evaluation due to the possibility that metastasis to an unusual anatomical site may occur.

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REFERENCES

1. **Berek JS, Karam A**. Vulvar cancer: epidemiology, diagnosis, histopathology, and treatment of rare histologies. UpToDate (15 May 2020). Available at: <https://www.uptodate.com/contents/vulvar-cancer-epidemiology-diagnosis-histopathology-and-treatment-of-rare-histologies>. Accessed: 20 May 2020.

2. **Mancini S, Bucchi L, Baldacchini F, *et al.*** Incidence trends of vulvar squamous cell carcinoma in Italy from 1990 to 2015. Gynecol Oncol 2020; **157**: 656–63.

3. **Weinberg D, Gomez-Martinez RA.** Vulvar cancer. Obstet Gynecol Clin North Am 2019; **46**: 125–35.

4. **Wakeham K, Kavanagh K, Cuschieri K, *et al.*** HPV status and favorable outcome in vulvar squamous cancer. Int J Cancer 2017; **140**: 1134–46.

5. **Hacker NF, Barlow EL.** Staging for vulvar cancer. Best Pract Res Clin Obstet Gynaecol 2015; **29**: 802–11.

6. **Singareddy R, Bajwa HK, Alluri KR, *et al.*** Carcinoma vulva patterns of recurrence and treatment outcomes: A single-institution experience. J Cancer Res Ther 2019; **15**: 1328–31.

7. **Vicus D, Korach J, Friedman E, *et al.*** Vulvar cancer metastatic to the breast. Gynecol Oncol 2006; **103**: 1144–6.

8. **Verfaillie G, Garbar C, Vanhoeij M, *et al.*** Metastasis of vulvar cancer in the breast. Acta Chir Belg 2012; **112**: 444–6.

9. **Bray F, Ferlay J, Soerjomataram I, *et al.*** Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin 2018; **68**: 394–424.

10. **Kang YJ, Smith M, Barlow E, *et al.*** Vulvar cancer in high-income countries: Increasing burden of disease. Int J Cancer 2017; **141**: 2174–86.

11. **Covens A, Vella ET, Kennedy EB, *et al.*** Sentinel lymph node biopsy in vulvar cancer: a systematic review, meta-analysis and guideline recommendations. Gynecol Oncol 2015; **137**: 351–61.

12. **Oonk MH, Planchamp F, Baldwin P, *et al.*** European Society of Gynaecological Oncology Guidelines for the management of patients with vulvar cancer. Int J Gynecol Cancer 2017; **27**: 832–7.

13. **Mahner S, Jueckstock J, Hilpert F, *et al.*** Adjuvant therapy in lymph node–positive vulvar cancer: the AGO-CaRE-1 study. J Natl Cancer Inst 2015; **107**: 1–12.

14. **Te Grootenhuis NC, Pouwer AFW, De Bock GH, *et al.*** Prognostic factors for local recurrence of squamous cell carcinoma of the vulva: A systematic review. Gynecol Oncol 2018; **148**: 622–31.

15. **Mota E, Mesquita IP, Pires C, *et al.*** Hypercalcemia and extensive chest metastasis of vulvar squamous cell carcinoma. Eur J Case Rep Intern Med 2019; **6**: 001218.

16. **Bizzarri N, Vellone VG, Parodi L, *et al.*** Cutaneous metastasis from vulvar squamous cell carcinoma: a rare occurrence that should not be forgotten. J Obstet Gynaecol 2017; **37**: 975–81.

17. **Seward SM, Richardson DL, Leon ME, *et al.*** Metastatic squamous cell carcinoma of the vulva to the lung confirmed with allelotyping. Int J Gynecol Pathol 2009; **28**: 497–501.

18. **Schumacher A, Rohde E.** Rare metastasis of vulvar cancers. Zentralbl Gynakol 1992; **114**: 379–81.

19. **Moreno-Astudillo L, Villaseñor-Navarro Y, Sánchez-Goytia V, *et al.*** A case series of breast metastases from different extramammary malignancies and their literature review. Case Rep Radiol 2019: **2019**: 9454201.

20. **Khouchani M, Benchakroun N, Tahri A, *et al.*** Breast metastasis from vulvar carcinoma: Case report and review of literature. Cancer Radiother 2008; **12**: 120–5.

21. **Bitencourt AG, Gama RR, Graziano L, *et al.*** Breast metastases from extramammary malignancies: multimodality imaging aspects. Br J Radiol 2017; **90**: 20170197.

22. **Honda M, Saji S, Horiguchi S, *et al.*** Clinicopathological analysis of ten patients with metaplastic squamous cell carcinoma of the breast. Surg Today 2011; **41**: 328–32.

23. **Parthasarathy A, Cheung MK, Osann K, *et al.*** The benefit of adjuvant radiation therapy in single-node-positive squamous cell vulvar carcinoma. Gynecol Oncol 2006; **103**: 1095–9.

24. **Landrum LM, Lanneau GS, Skaggs VJ, *et al.*** Gynecologic Oncology Group risk groups for vulvar carcinoma: improvement in survival in the modern era. Gynecol Oncol 2007; **106**: 521–5.

НЕЗВИЧАЙНИЙ ВИПАДОК РАКУ ВУЛЬВИ З МЕТАСТАЗАМИ В МОЛОЧНУ ЗАЛОЗУ

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Карцинома вульви є четвертим за поширеністю гінекологічним злоякісним новоутворенням. За попередніми оцінками, у 2020 р. у всьому світі буде зареєстровано понад 40 тис. нових випадків. Це захворювання характеризується локорегіональним поширенням з високою частотою рецидивів, при цьому віддалені метастази є рідкісним явищем. Метою даної роботи є опис діагностики, лікування та клінічного перебігу карциноми вульви у пацієнтки, у якої спостерігалися регіонарні рецидиви та пізні метастази в молочну залозу. Рак вульви — це захворювання з чітко визначеним перебігом, але з розвитком терапевтичних можливостей в останні роки стало можливим покращити прогноз, зни-