

Case report

What to do when nothing else is left to be done - metastatic non-HPV vulvar squamous cell carcinoma with multiple lines of chemotherapy

Mihaela Mărioara Stana^{1,*}, Sandra Deac¹, Călin Cainap^{2,3}, Patriciu Achimaș-Cadariu^{3,4}, Mădălina Bota⁵, Liliana Resiga⁶, Dan Ștefan Luchian⁷, Ovidiu Vasile Bochiș¹

¹"Ion Chiricuță" Oncologic Institute, Cluj-Napoca, Romania; ²Department of Oncology, "Iuliu Hatieganu" University of Medicine and Pharmacy, Cluj-Napoca, Romania; ³"Iuliu Hatieganu" University of Medicine and Pharmacy, Cluj-Napoca, Romania; ⁴Department of Surgery, "Ion Chiricuță" Oncologic Institute, Cluj-Napoca, Romania; ⁵Department of Mother and Child, "Iuliu Hatieganu" University of Medicine and Pharmacy, Cluj-Napoca, Romania; ⁶Pathology Department of "Ion Chiricuță" Oncologic Institute, Cluj-Napoca, Romania; ⁷Oncology Department of County Hospital Satu Mare, Romania

Abstract

Recurrent vulvar squamous cell carcinoma with multiple site metastases is a rare entity – (up to 14.2% of the total number of recurrences), with a poor prognosis (only 15% of the patients alive at 5 years). Due to its "hard to find" character, there are no standardized guidelines available and the treatment is extrapolated from advanced cervical carcinoma, anal carcinoma and other squamous cell carcinomas. Immunotherapy has shown some positive results in vulvar carcinoma with PD-L1 positive, high TMB, high MSI or with MMR deficiency. An alternative for selected cases without therapeutic resources could be the HPV vaccine. We present the case of a 64-year-old woman diagnosed in 2014 with vulvar squamous cell carcinoma stage II for which she underwent radical vulvectomy with bilateral inguinal lymphadenectomy followed by external radiotherapy. In 2019 she developed local recurrence associated with lung, pleural, lymph nodes and subcutaneous metastasis, treated with three lines of chemotherapy: paclitaxel/carboplatin followed by cisplatin/5-fluorouracil and carboplatin/gemcitabine. The patient's general health status altered progressively, and she died after the 4th cycle of carboplatin/gemcitabine. This case's management could be a starting point for the vulvar carcinoma cases where the standard therapeutical options do not represent a choice anymore, providing the necessary example on how to approach it.

Keywords: *vulvar squamous cell carcinoma; recurrence; HPV; chemotherapy*

Introduction

Vulvar squamous cell carcinoma (VSCC) represents up to 5% of female genital carcinomas [1]. The "gold standard" for early-

stage cases is represented by surgery, but this therapeutic approach is associated with multiple adverse events. In more advanced cases, external beam radiation therapy (EBRT) is used in association with brachytherapy to consolidate the surgical results or even to replace surgery in selected cases with contraindications or technical challenges. The long-term results are comparable to the surgical approach [1].

Received: August 2021; Accepted after review: September 2021; Published: September 2021.

*Corresponding author: Mihaela Mărioara Stana, "Ion Chiricuță" Oncologic Institute, 34-36 Republicii Street, Cluj-Napoca, Romania.

Email: zahari_mihaela2000@yahoo.com



For advanced cases, the treatment options are limited. A metastatic case is considered from the beginning with a poor prognosis due to the lack of clinical trials available. The reason behind the lack of evidence is the rarity of this tumor worldwide [1, 2]. In vulvar carcinoma, the most common is lymphatic dissemination, the inguinal lymph nodes being the first station of spread. The hematogenous pathway of distant dissemination occurs in the late stages [3].

Targeted therapy and immunotherapy had revolutionized the oncology field in many solid and hematologic malignancies, but these options have not yet proven effective in VSCC.

Therefore, research of novel therapies is mandatory [1, 3].

Case report

We present the case of a 64-year-old woman who was treated in April 2014 for a 10 cm hard, bloody, warty and brittle lesion on the right labium that blocked the vaginal canal. Bilateral inguinal lymphadenopathies were associated.

The biopsy revealed a squamous cell vulvar carcinoma, Human Papilloma Virus (HPV) independent (Figure 1).

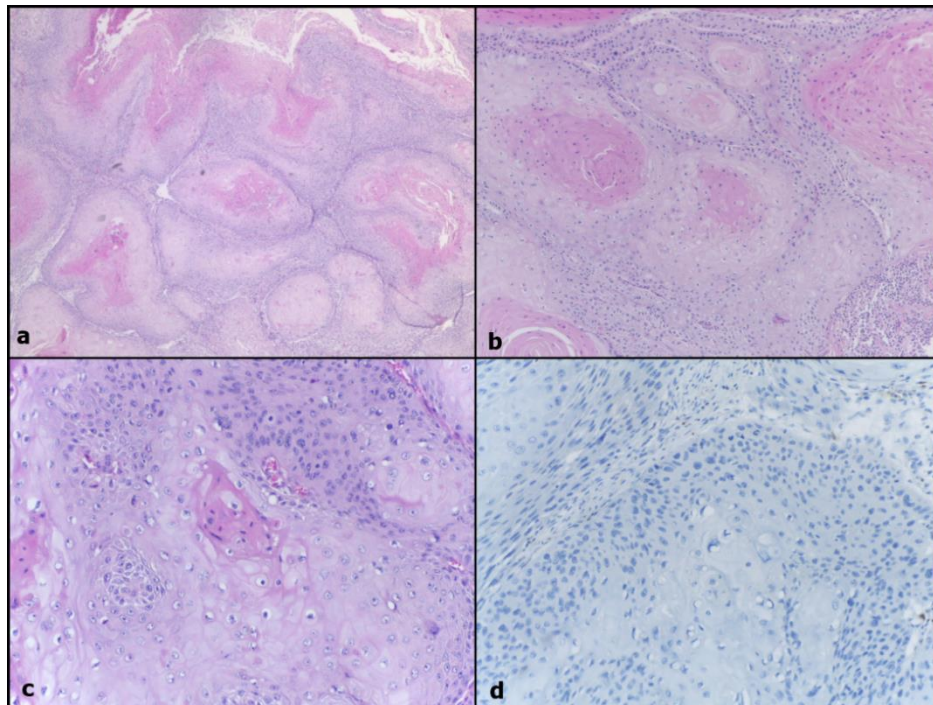


Fig. 1. HPV independent vulvar squamous cell carcinoma G1: a. back-to-back nests of well differentiated squamous epithelium with massive hyperkeratosis and parakeratosis (HE, x40); b. moderate chronic inflammation in stroma (left bottom) (HE, x100); c. abundant pale, eosinophilic cytoplasm with low nuclear to cytoplasmic ratio, mild nuclear pleomorphism, basally located mitotic figures (HE, x200); d. negative p16 in tumor cells (IHC, anti-p16 antibody, x200).

The patient underwent radical vulvectomy with bilateral inguinal lymphadenectomy. The histopathology result confirmed a vulvar squamous cell carcinoma, well-differentiated, pT₂N₀M_xL₀V₀R₀, cM₀, stage II. To consolidate the surgical results, EBRT (total dose = 45 Grey/18 fractions/33 days) was performed between July 2014 and September 2014, without concomitant chemotherapy. The delay

between EBRT fractions was due to technical issues.

Her family oncologic history was insignificant. The menarche was installed at the age of 18 and the last menstruation was at the age of 46 (surgically induced). She was G2P1. The patient had the following associated comorbidities: grade II mitral valve insufficiency, grade I tricuspid valve

insufficiency, chronic venous insufficiency, endometrial hyperplasia and endometriosis for which she underwent total hysterectomy with bilateral adnexectomy in 2001.

Five years later, in September 2019, the patient (now 64 years old) developed local recurrence with massively infected areas of

the tumor mass. A thorax-abdominal-pelvic CT (TAP CT) with contrast was performed and revealed local recurrence in the pelvis, left inguinal lymphadenopathies and multiple nodular subcutaneous lesions in the abdominal wall, suggesting progressive disease (Figures 2a and 2b).

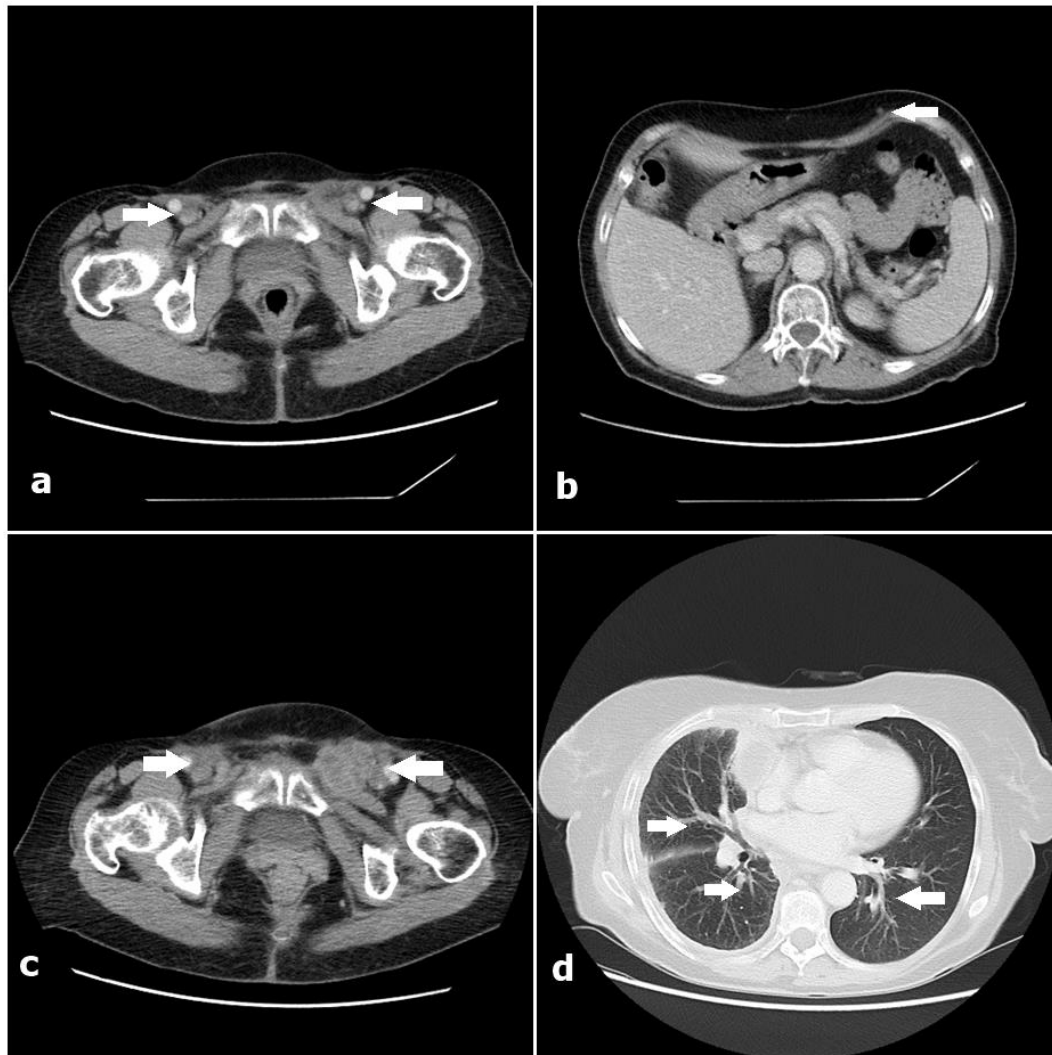


Fig. 2. Axial CT scan sequences, venous phase: a) bilateral inguinal lymph nodes (white arrows) December 2019; b) abdominal wall subcutaneous metastasis (white arrow) December 2019; c) increased bilateral inguinal lymph nodes (white arrows) April 2020; d) bilateral lung metastasis and right lung lymphangitis (white arrows) April 2020.

The case was addressed to the multidisciplinary team of our oncologic center. The surgical consult sustained the inoperable status and the radiotherapy specialist decided that re-irradiation of the pelvic area is not a therapeutic option. With the goal of conversion to operability, 1st line metastatic chemotherapy with Paclitaxel 175 mg/m²/qw3 and Carboplatin 5 AUC/qw3 (TC) was started in

December 2019. The patient received 3 cycles of this systemic treatment with good tolerance; she complained of minimal arthralgia and myalgia in the 1st-4th days post chemotherapy which responded to 1st step pain relief treatment. First grade thrombocytopenia was also identified.

In February 2020, the gynecologic and surgical consult concluded that the disease

has extended to the anal sphincter (local disease progression) and subsequently, 2nd line metastatic chemotherapy was started with Cisplatin 100 mg/m²/day 1 q3w and 5-fluorouracil 1000 mg/m²/days 1-4 q3w (PF). The first 2 cycles have been well tolerated. Only mild fever (38.1 °C) on the 1st day, lack of appetite in the first 3 days and grade I normochromic normocytic anemia were observed. Febrile neutropenia primary prophylaxis with subcutaneous G-CSF was performed. For the 3rd cycle of PF, the patient presented with nausea, vomiting and right hypochondrium pain. The chemotherapy was postponed until further information was obtained.

The abdominal ultrasound (US) was normal. To control the painful symptoms, 2nd step pain relief treatment has been initiated and the pain was relieved with the administration of the 3rd cycle.

In April 2020, when the next cycle of treatment was due to be administered, the patient accused lumbar pain for 2 days. At the objective exam, on the right hemi thorax, the

vesicular murmur and the pectoral fremitus were diminished.

A pulmonary X-ray revealed mild to moderate right pleural effusion with bilateral pulmonary interstitium highlighted. We decided to perform a TAP CT scan with contrast which revealed bilateral pulmonary metastasis, tumor pleural thickening, right lung carcinomatous lymphangitis and bilateral inguinal and external iliac lymphadenopathies (Figures 2c and 2d).

After we diagnosed the pulmonary and lymph nodes disease progression, 3rd line metastatic chemotherapy was started with Gemcitabine 1250 mg/m²/days 1, 8 q3w and Carboplatin AUC 5/day 1 q3w. After the 1st cycle, the stool was pencil-shaped with accentuation of the lumbar pain and general health status alteration. Due to logistic issues and the patient's decision, the treatment was continued at the local Oncology Department. Four more cycles of Gemcitabine and Carboplatin were eventually given, until the patient's death in July 2020 (Figure 3).

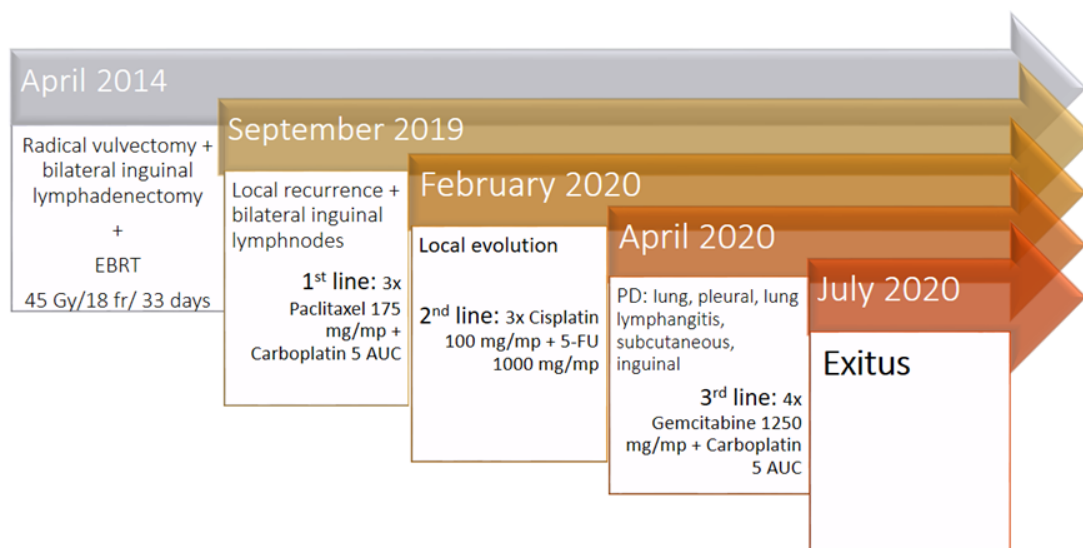


Fig. 3. Case management outline for metastatic vulvar squamous cell carcinoma

Discussion

Vulvar carcinoma is a rare solid tumor, accounting for up to 3-5% of gynecological malignancies and 1% of all types of tumors in women. The typical presentation is the

postmenopausal women in the sixth or seventh decade of life who accuses vulvar pruritus and a painful and/or bleeding vulvar tumor. Squamous histological subtype is the most common, about 90% of all vulvar cancers [4].

HPV infection, nicotine addiction, chronic skin inflammation such as lichen sclerosus or lichen planus and immunocompromised conditions are the most known risk factors for vulvar cancer [5, 6].

HPV-independent vulvar carcinomas develop in older women. They arise under an inflammatory skin disorder and a type of in situ lesions known as differentiated intraepithelial neoplasia. It is proved that p16 immunohistochemistry is a good substitute marker for HPV presence. Ideally, the HPV DNA test is the standard for detecting HPV infection, but the IHC is often sufficient.

HPV-positivity is associated with a less aggressive tumor [7]. Thus, the lack of response after the first-line chemotherapy regimen could be sustained by the HPV-negative tumor type known for its aggressive pattern and resistance to treatment.

We presented the case of a multisite metastatic recurrent vulvar squamous cell carcinoma HPV-independent and we highlighted the rarity of this clinical expression: about 5% of the patients with vulvar carcinoma develop distant metastasis [3].

In the treatment of vulvar carcinoma, surgery is the most used method, radical vulvectomy being the standard of care. An alternative to radical surgery is wide local excision with sentinel lymph node biopsy, to which an inguinal lymphadenectomy can be added.

Radiotherapy is part of the vulvar carcinoma treatment strategy being used in the preoperatively or postoperatively setting or as the only therapeutic option in locally advanced disease with bulky tumor or lymph nodes invasion [2]. In our case, according to radiobiology, a reason for the recurrence might have been the large interval between EBRT fractions (which gave to the tumor cells time to re-divide) and the lack of concomitant chemotherapy (which would have offered a better disease control).

New techniques in radiotherapy, such as intensity-modulated radiotherapy (IMRT) reduce the radiation doses to normal tissues. As toxicity is reduced, the treatment is more tolerable and there is no need to interrupt the treatment and to endanger the local treatment's results [8].

In the case of distant metastases, we believe that the tumor cells are spreading through hematogenous pathway, most commonly in the lungs, liver and bones [3]. Even if systemic regimens can have high toxicities, in our case the patient tolerated them relatively well. Despite its good tolerance, after first-line treatment in the metastatic stage, cancer had an accelerated evolution.

Systemic treatment like chemotherapy is not well studied in vulvar carcinoma patients. The chemotherapy regimens are used by extrapolation from advanced cervical carcinoma and anal carcinoma, without any standardized scheme. In metastatic or recurrent cancers, the most recommended regimens are based on: cisplatin or carboplatin monotherapy or cisplatin/paclitaxel, carboplatin/paclitaxel and cisplatin/paclitaxel/bevacizumab. Alternatives for second line therapy are: paclitaxel monotherapy, erlotinib (category 2B), cisplatin/vinorelbine, cisplatin/gemcitabine (category 2B), carboplatin/paclitaxel/bevacizumab (category 2B). Immunotherapy with pembrolizumab has a tissue-agnostic recommendation in MSI-high/MMR deficient tumors [9].

In Romania, bevacizumab, erlotinib or immunotherapy are not reimbursed in vulvar cancer, so the only option to obtain some disease control was chemotherapy. We chose a combined chemotherapy in the detriment of monotherapy due to the initially good general health status of the patient, in hope for a better tumor response. However, the tumor was chemoresistant despite the use of the best available therapeutic options at that time.

The prophylactic effect of HPV vaccine is almost 100% for premalignant lesions, but without providing certainty for established infection, dysplasia, or carcinoma. In some critical circumstances, vaccinating a patient out of other therapeutic options might bring a chance to prolong survival [10].

The presented case highlights the steps taken to obtain the best quality of life for this patient and helps the oncology field to create an opinion on how to proceed for the cases not found in the books.

Conclusion

Distant recurrence of vulvar carcinoma is infrequent. Providing the best supportive care is always a feasible option, but the use of systemic chemotherapy is worth trying in particular cases.

Despite the lack of clinical trials and category 1 chemotherapy recommendations at this stage of the disease, the case presented may be an example for the management of recurrent squamous cell carcinoma, independent of HPV, treated with three lines of chemotherapy. We provide valuable information for vulvar cancer therapy.

The patient's survival interval starting from local recurrence diagnostic was 11 months. It was a period during which we applied our best knowledge as tertiary oncologic center. We want to share the acquired knowledge as adopting a successful therapeutic scheme is

important for this small, but important, category of women with metastatic vulvar carcinoma.

Informed Consent

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

Credit authorship contribution statement

Mihaela Marioara Stana: Writing - original draft, Writing - review & editing. Sandra Deac: Writing - review & editing. Calin Cainap: review & editing, Patriciu Achimas-Cadariu: surgery & review, Madalina Bota: review & editing. Liliana Resiga: pathology & review, Dan Stefan Luchian: treated the patient & review, Ovidiu Vasile Bochis: Treated the patient, Supervision, Writing - review & editing.

Competing Interest:

Nothing to declare.

References

1. Clancy AA, Spaans JN, Weberpals JI. The forgotten woman's cancer: vulvar squamous cell carcinoma (VSCC) and a targeted approach to therapy. *Ann Oncol* 2016; 27(9):1696-1705. <https://doi.org/10.1093/annonc/mdw242>
2. Zobec Logar HB. Long term results of radiotherapy in vulvar cancer patients in Slovenia between 1997-2004. *Radiol Oncol* 2017; 51(4):447-454. <https://doi.org/10.1515/raon-2017-0024>
3. Peri M, Grassadonia A, Iezzi L, et al. A case of stage I vulvar squamous cell carcinoma with early relapse and rapid disease progression. *Case Rep Oncol Med* 2019; 2019:1018492. <https://doi.org/10.1155/2019/1018492>
4. Papatheodorou DC, Liakou CG, Kalogerakos K, Dimopoulos JKA, Kalinoglou N. Bilateral breast metastases from vulvar carcinoma: a case report and literature review. *Case Rep Obstet Gynecol* 2017; <https://doi.org/10.1155/2017/1357203>
5. Syed IMJ, Naveed A, Salman F, Faizan M, Mark S. The tell-tale heart: A case of recurrent vulvar carcinoma with cardiac metastasis and review of literature. *Gynecol Oncol Rep* 2017; (21):20-23. <https://doi.org/10.1016/j.gore.2017.06.004>
6. Woelber L, Jaeger A, Prieske K. New treatment standards for vulvar cancer 2020. *Curr Opin Obstet Gynecol* 2020; 32(1):9-14. <https://doi.org/10.1097/GCO.0000000000000595>
7. Rakislova N, Saco A, Sierra A, Del Pino M, Ordi J. Role of Human Papillomavirus in vulvar cancer. *Adv Anat Pathol* 2017; 24(4):201-214. <https://doi.org/10.1097/PAP.0000000000000155>
8. Deppe G, Mert I, Belotte J, Winer IS. Chemotherapy of vulvar cancer: a review. *Wien Klin Wochenschr* 2013; 125(5-6):119-128. <https://doi.org/10.1007/s00508-013-0338-y>
9. NCCN Guidelines Version 2 .2021. Vulvar Cancer (Squamous Cell Carcinoma). Information [https://www.nccn.org/professionals/physician_gls/pdf/vulvar.pdf available at 09/30/2021]
10. Gustafson LW, Gade M, Blaakær J. Vulvar cancer and HPV vaccination in recurrent disease. *Clin Case Rep* 2014; 2(6):243-246. <https://doi.org/10.1002/ccr3.93>

