Case report

Biventricular cardiac metastasis from vulvar squamous cell carcinoma

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Abstract

Vulvar cancers make up just 3% to 5% of all gynecological cancers, and they are most typically found in postmenopausal women. Vulvar cancer distant metastases are uncommon and usually arise late. Only six cases of vulvar cancer metastasizing to the heart have been reported in the literature, and none of them included both the left and right ventricles. We describe the case of a 68-year-old patient diagnosed with vulvar cancer arising from lichen sclerosus, initially localized, treated with chemotherapy, surgery, and radiation therapy. Less than two months after the end of the treatment sequence, the patient returned to our clinic with bone pain. Imaging investigations have shown multiple disseminated metastases, but not in the heart at that moment. Chemotherapy was initiated, and after two cycles, the patient developed an arrhythmia (atrial fibrillation with rapid ventricular rate), which was later determined to be caused by cardiac metastases discovered by echocardiography and computed tomography. Vulvar cancer metastatic to the heart represents a rare clinical condition, requiring multidisciplinary care. The case's uniqueness is the biventricular metastasis, which resulted in STEMI despite angiographically normal epicardial coronary arteries.

Keywords: *vulvar squamous cell carcinoma; cardiac metastasis; natural history; heart arrhythmia*

Introduction

After cervical, ovarian, and uterine corpus cancer, vulvar cancer is the fourth most frequent gynecologic cancer in highly industrialized countries [1]. It represents approximately 5% of malignancies in the female genital tract [1]. As histologic subtypes, the most common is squamous cell carcinoma (SCC). Other histological types include sarcoma, melanoma, basal cell carcinoma, adenocarcinoma or neuroendocrine tumors [2].

The risk factors include vulvar or cervical intraepithelial neoplasia, a prior history of cervical cancer, vulvar lichen sclerosus, immunodeficiency syndromes, smoking and northern European ancestry [3]. Infection with human papillomavirus (HPV) is associated with 28.6% of invasive vulvar cancer cases. HPV 16 was the most common subtype (72.5%), followed by HPV 33 (6.5%) and HPV 18 (4.6%) [3–5].

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There are two main pathways of metastasis for vulvar cancer: lymphatic spread – that is the main route of spreading the disease, and hematogenous dissemination - which is less frequent, especially in patients without regional lymph node involvement [6].

Cardiac metastases occur more than 20 times more often than primary cardiac tumors which, in general, are found incidentally [7]. For example, in a series of autopsies on more than 1900 cancer patients, 8% of them had metastasis in the heart [8]. Cardiac involvement in vulvar cancer may arise from hematogenous metastases, which can be either symptomatic or asymptomatic.

In this report, we describe a patient with vulvar squamous cell carcinoma associated with lichen sclerosus, who had a quick progression of the disease. Almost a year after the diagnosis, we discovered multiple myocardial lesions localized in both the left and right ventricle. These masses invaded the pericardium. As far as we know, this is the first recorded case of a patient with vulvar cancer and metastases in both the right and left ventricles.

Case report

A 68-year-old woman with a past medical history of lichen sclerosus and polyallergy was admitted in our clinic in November 2020 with perineal pain, itching and bleeding in the vulvar region. Gynecological examination revealed an advanced, exophytic, imprecisely delineated, hard, mobile, but sensitive to palpation locoregional tumor, measuring approximately 50/30 mm. Also, bilateral vulvar lymphadenopathy has been identified on clinical examination.

The patient was of Eastern European descent and was a non-smoker. The patient's mother died of breast cancer at the age of 50. She had two pregnancies and two births, and menopause was at the age of 51.

The patient underwent pelvic magnetic resonance imaging (MRI) examination that showed a tumor belonging to the left labia minora, without obvious invasion of the adjacent perineal structures. Bilateral inguinal lymph nodes were also discovered, the largest (7 mm) was present on the left side and it was suspicious for malignancy.

A tumor biopsy was then performed. It identified vulvar keratinizing squamous cell carcinoma, well-differentiated (G1), unassociated with HPV infection, p16 and p53 negative (Figure 1).

She performed chest-abdomen staging tomography that ruled out the presence of metastasis at this moment.

Consequently, the patient was initially staged as cT2N1bM0, FIGO IIIA and it was decided to initiate induction chemotherapy based on Paclitaxel and Carboplatin, followed by total vulvectomy with bilateral inguinal lymphadenectomy and adjuvant external radiotherapy.

In December 2020, chemotherapy was started, which was performed for only 2 cycles because the patient did not tolerate the administration of paclitaxel due to an allergic reaction.

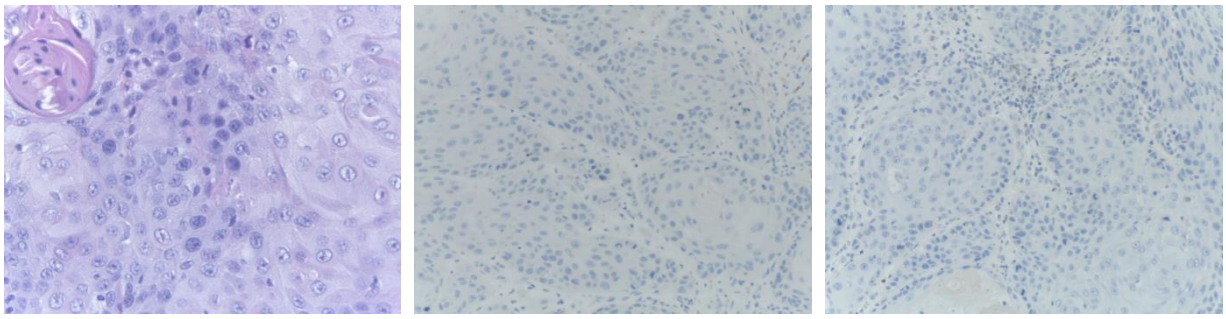

Fig. 1. Histological examination of the tumor. A. vulvar keratinizing squamous cell carcinoma, well differentiated (HE, x400); B. p16 negative in tumor cells (IHC, anti-p16 Ab, x200); C. Negative p53 in tumor cells (IHC, anti-p53 Ab, x200).

After that, it is decided in January 2021 to perform total vulvectomy, initially without lymphadenectomy. After the pathological result, ypT1bNxV0L1Pn0R0, due to the lymphatic invasion (L1) and negative resection margin (R0), surgical re-intervention was decided to complete with bilateral inguino-femoral lymphadenectomy. Of the 39 lymph nodes examined, none were metastatic (ypN0).

The case was presented at this time in the tumor board which recommends external radiotherapy and chemotherapy for radiosensitizing purposes. The latter could only be given in a single cycle of Cisplatin due to the general toxicity. Radiation therapy was performed between May and June 2021, with 50.4 Gy/28 fractions being administered to the vulva and the pelvic and inguinal lymph nodes bilaterally. She developed grade 2 radiodermatitis after the radiation.

The patient was imagistically re-evaluated in August 2021 because of the presence of new right knee pain and diffuse, low intensity abdominal pain. Those investigations revealed metastasis in the lungs, pleura, liver, retroperitoneum, left adrenal gland, bone, lymph nodes and muscle.

It was decided to start chemotherapy with vinorelbine, carboplatin and zoledronic acid, and to perform analgesic radiotherapy on the right tibial plateau with a dose of 20 Gy/5 fractions.

In September, when she was scheduled for the 2nd cycle of cytostatic treatment, the patient returned to our clinic with sinus tachycardia (95 beats per minute) which was interpreted in the context of anemia (hemoglobin 8.5 g/dl). Beta-blocker treatment was initiated and erythrocyte mass transfusion was administered.

Next month, the patient showed up on schedule, but in addition, she had shortness of breath on exertion. The objective examination revealed pulmonary rales of stasis at the basal, bilateral level and tachycardic heart sounds (about 90-95 beats per minute), intermittently arrhythmic. During hospitalization, she had several episodes of atrial fibrillation with rapid ventricular rate, which spontaneously converted to sinus rhythm. Systematic treatment with beta-blocker and a parenteral anticoagulant with fractionated heparin were initiated.

On the following day, the patient presented ST-segment elevation in the lateral leads on the electrocardiogram (ECG), with just mild chest pain - probably because she was receiving chronic analgesic treatment with a morphine derivative. Myocardial necrosis markers (troponin I, CK and CK-Mb) were elevated, which is why we decided to transfer the patient to a specialized cardiology clinic for further investigations. There, the case was interpreted as acute myocardial infarction with lateral ST segment elevation (lateral STEMI), with about 2 hours duration. The transthoracic echocardiography in the emergency room revealed, from the subcostal view, two great inhomogeneous masses in the right ventricular free wall and from the apical 4-chamber view another great inhomogeneous mass in the lateral left ventricular wall, with pericardial invasion (Figure 2). Both ventricles had a normal systolic function. Due to the known oncological pathology and the echocardiographic aspect, there was raised suspicion of cardiac metastasis.

An emergency cardiac computer tomography scan was performed (Figure 3), which revealed at least 4 inhomogeneous lesions at the myocardial level, the greatest with dimensions up to 54/43 mm, with probable pericardial invasion, located both in the left and in the right ventricle.

After that, because the patient's acute problem was interpreted as lateral STEMI, an emergent coronary angiography was performed. No obstructive epicardial coronary lesions were found.

During hospitalization in the coronary intensive care unit, the patient was anginal pain free and remained in atrial fibrillation. After 1200 mg intravenous amiodarone the patient was converted in sinus rhythm and continue the treatment with amiodarone, beta-blocker and anticoagulant. After 24 hours in the coronary intensive unit, the patient was transferred to the Oncology Department. It was decided to continue only with best supportive care. In about a month, the patient died. Figure 4 summarizes the sequence of the patient's disease over time, including the treatments performed.

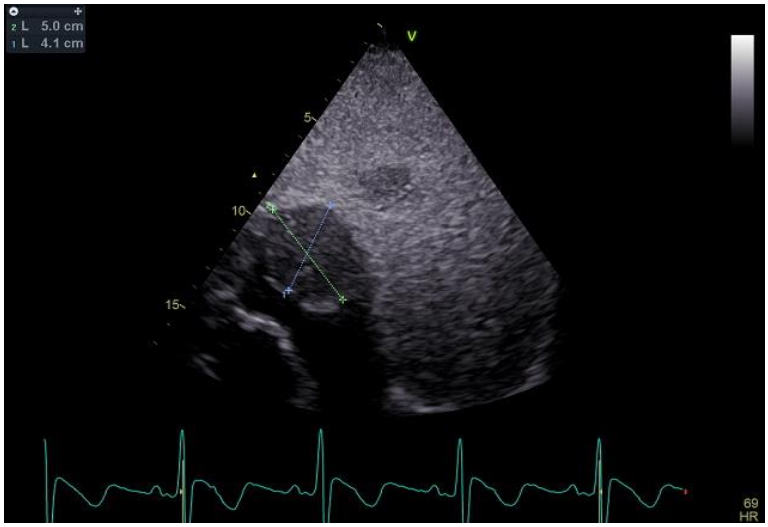

Fig. 2. Giant metastases in the right ventricle 50/41 mm (subcostal view).

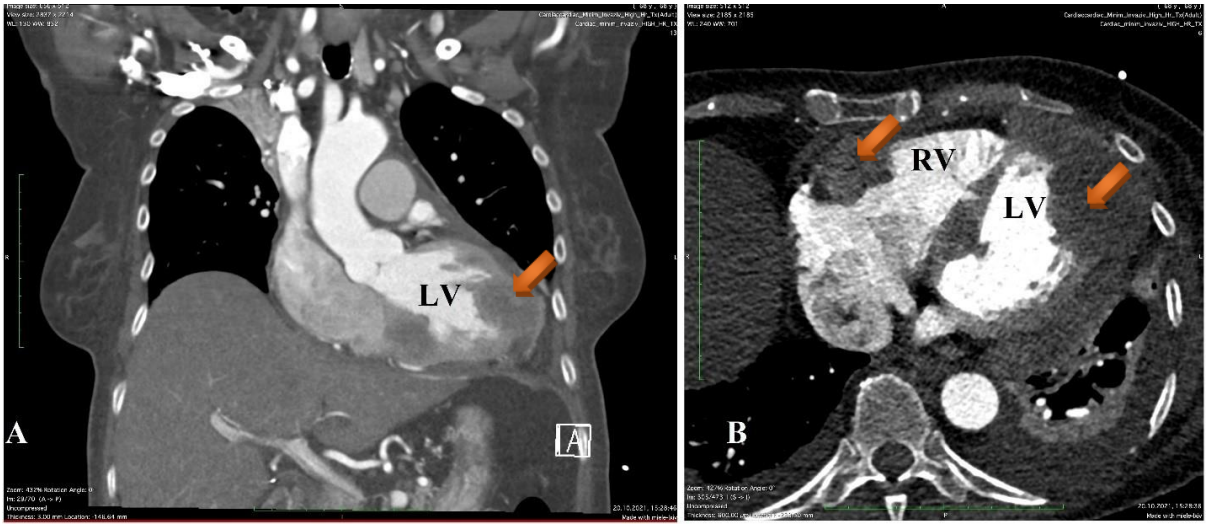

Fig. 3. Cardiac Computed Tomography with contrast. A. Coronal section of the heart– lesions in the left ventricle (*arrow)*. B. Axial section – metastasis in both parts of the heart (*arrows)*.

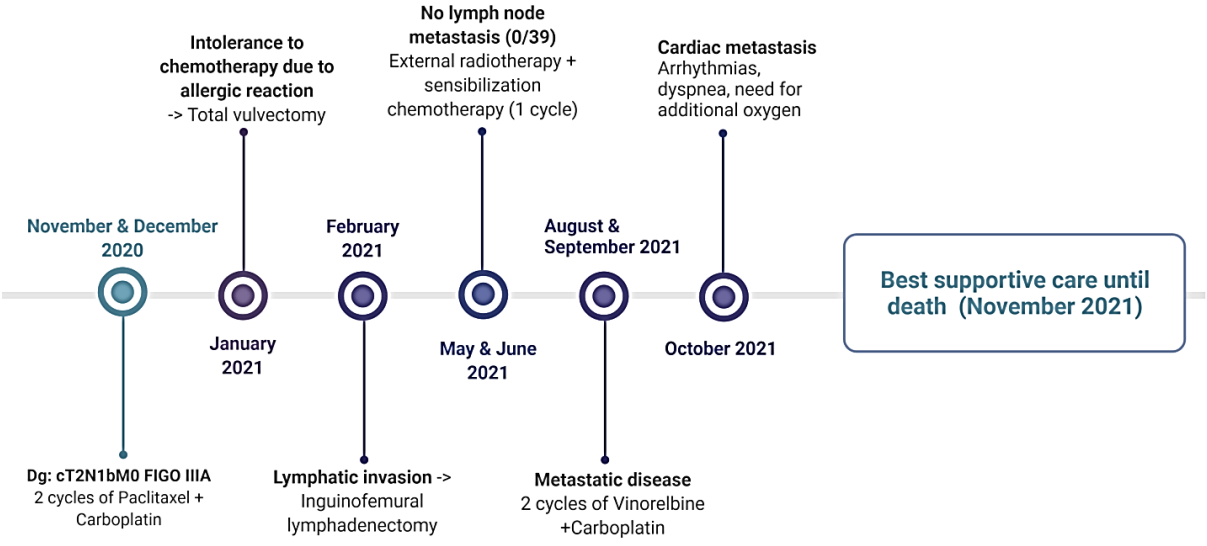

Fig. 4. Treatment history and timing onset of cardiac symptoms of a metastatic vulvar cancer patient.

Discussions

Vulvar cancer is a rare malignancy, with an annual incidence of 2-3 cases per 100,000 women. In the United States of America, there are near 6,330 of new cases and about 1,560 deaths from vulvar cancer per year [9]. Most patients with vulvar cancer are diagnosed at an early stage of disease and the signs and symptoms of all histologic types of vulvar malignancy are almost similar. At the time of diagnosis, many patients may be asymptomatic, but some of them can present with bleeding or local pruritus [10]. Although our patient presented with both preneoplastic changes (lichen sclerosus) and the typical symptoms of pruritus and hemorrhage, she presented to the doctor very late, only when the pain was significant, which led to a late diagnosis of an advanced stage of the disease. The magnitude of the vulvar lesion, the lymph node examination, and the presence of metastasis all influence how vulvar carcinoma is treated [10].

Malignant heart tumors account for about 15% of all heart tumors. Of these, the most common are sarcomas [11]. In contrast to primary malignancies, metastatic tumors are relatively common. The most frequent cancers that can metastasize to this level are melanomas, bronchopulmonary cancer, breast cancer, soft tissue sarcomas, esophageal cancer, hepatocellular carcinoma, kidney cancer, thyroid cancer and even lymphomas and leukemias [12, 13].

Cardiac or pericardial metastases should be considered when a patient who has a neoplasm develops pericardial effusion or any cardiovascular symptoms or clinical signs such as changes in the auscultation of the heart or arrhythmias recorded by the ECG [14].

When a heart tumor is suspected, imaging methods should be used to identify and characterize it. The initial investigation to be performed is echocardiography. Additionally, cardiac magnetic resonance imaging, computed tomography, and positron emission tomography are useful in certain circumstances [15]. In this study, cardiac symptoms and changes in ECG examinations led to further investigations, such as cardiac ultrasound and cardiac computed tomography, which confirmed the cause of her clinical manifestations.

To date, six cases of metastatic vulvar cancer of the heart have been published in the medical literature. Of these, four had a tumor located on the right side and two - on the left. [16–21]. The peculiarity of our case is that the patient had four myocardial tumors, with pericardial invasion, located in both ventricles, which led to ST segment elevation on the surface ECG, the patient being first interpreted as a patient with STEMI.

The inability to obtain a histopathologic sample confirmation from the cardiac masses was one of the limitations of the present case. But, because of the poor prognosis, a cardiac biopsy might not change anything in the management of the disease. However, the previous cardiac examinations have not revealed any signs of masses in the heart (the patient's last transthoracic echocardiography was one month before the cardiac manifestation). Arguments for features of metastatic spread are the characteristics of the masses on the echocardiogram and on computed tomography described earlier (confluent, irregular masses localized in left and right ventricles with the invasion of the pericardium).

Conclusions

This case shows an aggressive form of vulvar cancer that metastasizes to different organs. The particularity of the case represents the invasion of both ventricles that generated STEMI with angiographically normal epicardial coronary arteries and with minimal painful symptoms. The importance of a multidisciplinary team is crucial in managing such cases because the natural history of cancer can follow an atypical course. The revealing symptoms of some metastatic sites always require a clinical and paraclinical differentiated diagnosis.

Abbreviations

ECG: electrocardiogram;
HPV: human papillomavirus;
IHC: immunohistochemistry;

MRI: magnetic resonance imaging;
SCC: squamous cell carcinoma;
STEMI: ST-elevation myocardial infarction;

Competing interests

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Consent for publication

All procedures performed in this study were in accordance with the standards of ethical research and written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal.

References

1. ECIS – European Cancer Information System Information Page [https://ecis.jrc.ec.europa.eu available at 05.25.2022].
2. Wohlmuth C, Wohlmuth-Wieser I. Vulvar malignancies: an interdisciplinary perspective. *J Dtsch Dermatol Ges*. 2019; 17(12):1257–1276. doi:10.1111/ddg.13995
3. Bucchi L, Pizzato M, Rosso S, Ferretti S. New insights into the epidemiology of vulvar cancer: systematic literature review for an update of incidence and risk factors. *Cancers (Basel).* 2022; 14(2):389. doi:10.3390/cancers14020389
4. de Sanjosé S, Alemany L, Ordi J, et al. Worldwide human papillomavirus genotype attribution in over 2000 cases of intraepithelial and invasive lesions of the vulva. *Eur J Cancer*. 2013; 49(16):3450–3461. doi:10.1016/j.ejca.2013.06.033
5. van de Nieuwenhof HP, Bulten J, Hollema H, et al. Differentiated vulvar intraepithelial neoplasia is often found in lesions, previously diagnosed as lichen sclerosus, which have progressed to vulvar squamous cell carcinoma. *Mod Pathol*. 2011; 24(2):297–305. doi:10.1038/modpathol.2010.192
6. Hacker NF, Berek JS, Lagasse LD, Leuchter RS, Moore JG. Management of regional lymph nodes and their prognostic influence in vulvar cancer. *Obstet Gynecol*. 1983; 61(4):408–412. PMID: 6828268
7. Reynen K. Frequency of primary tumors of the heart. *Am J Cardiol*. 1996; 77(1):107. doi:10.1016/s0002-9149(97)89149-7
8. Silvestri F, Bussani R, Pavletic N, Mannone T. Metastases of the heart and pericardium. *G Ital Cardiol*. 1997; 27(12):1252–1255. PMID: 9470058
9. Siegel RL, Miller KD, Fuchs HE, Jemal A. Cancer statistics, 2022. *CA Cancer J Clin*. 2022; 72(1):7–33. doi:10.3322/caac.21708
10. Tan A, Bieber AK, Stein JA, Pomeranz MK. Diagnosis and management of vulvar cancer: A review. *J Am Acad Dermatol*. 2019; 81(6):1387–1396. doi:10.1016/j.jaad.2019.07.055
11. Molina JE, Edwards JE, Ward HB. Primary cardiac tumors: experience at the University of Minnesota. *Thorac Cardiovasc Surg*. 1990; 38(Suppl 2):183–191. doi:10.1055/s-2007-1014064
12. Savoia P, Fierro MT, Zaccagna A, Bernengo MG. Metastatic melanoma of the heart. *J Surg Oncol.* 2000; 75(3):203–207. doi:10.1002/1096-9098(200011)75:3<203::aid-jso9>3.0.co;2-x
13. Goldberg AD, Blankstein R, Padera RF. Tumors metastatic to the heart. *Circulation*. 2013; 128(16):1790–1794. doi:10.1161/CIRCULATIONAHA.112.000790
14. Sosinska-Mielcarek K, Senkus-Konefka E, Jassem J, Kulczycka J, Jendrzejewski J, Jaskiewicz K. Cardiac involvement at presentation of non-small-cell lung cancer. *J Clin Oncol.* 2008; 26(6):1010–1011. doi:10.1200/JCO.2007.14.9328
15. Bussani R, Castrichini M, Restivo L, et al. Cardiac tumors: diagnosis, prognosis, and treatment. *Curr Cardiol Rep*. 2020; 22(12):169. doi:10.1007/s11886-020-01420-z
16. Hanbury WJ. Secondary tumours of the heart. *Br J Cancer*. 1960; 14(1):23–27. doi:10.1038/bjc.1960.3
17. Htoo MM, Nanton MA. Complete heart block due to disseminated vulval carcinoma. *Br Heart J.* 1973; 35(11):1211-1213. doi:10.1136/hrt.35.11.1211
18. Jafri SIM, Ali N, Farhat S, Malik F, Shahin M. The tell-tale heart: A case of recurrent vulvar carcinoma with cardiac metastasis and review of literature. *Gynecol Oncol Rep*. 2017; 21:20–23. doi:10.1016/j.gore.2017.06.004
19. Linder R, Lauterbach R, Reiss A. A case of recurrent vulvar carcinoma with cardiac metastasis: case report and review of the literature. *Int J Gynecol Pathol*. 2020; 39(4):400-403. doi:10.1097/PGP.0000000000000624
20. Nair RM, Thapa B, Maroo A. Left-sided intracardiac tumors in a case of widespread vulvar cancer. *JACC: Case Reports*. 2019;

1(2):179–183. doi:10.1016/j.jaccas.2019.05.029

21. Pablo P, Barbara M, Kanak P, Del Rio-Pertuz G, Sethi P, Shurmur S. Vulvar cancer with metastasis to the left ventricle: an unusual cause of electrocardiographic changes-a case report. *J Am Coll Cardiol*. 2021; 77(18):2613. doi:10.1016/S0735-1097(21)03968-1