

Accepted: February 21st 2022

REVIEW

Muscle-skeletal metastatic pattern in vulvar cancer

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Abstract

Vulvar cancer is a rare malignancy of the genital tract, the fourth most common type in this category. The most common form of the clinical appearance is long-lasting pruritus, a lump or mass on the vulva. Despite its histological type, in most cases, invasive vulvar cancer metastasizes primarily through the lymphatic system. Bone metastases related to gynecological cancers are rare, often underdiagnosed, and have a very poor prognosis. The most common site of metastasis in vulvar cancer is the lung, which is affected in about 45%, followed closely by the liver and brain. Bone metastases are present in about 10% to a quarter of cases. The most common places are the spine, pelvic bone, ribs, skull, limb bones and sternum. The only characteristic of the bone microenvironment is its high sensitivity to endocrine status, as vulvar cancer affects postmenopausal women. Thus, the theory of the protective role of estrogen on bone density and bone metastases remains an open door for future protection and treatment strategies.

Keywords: vulvar cancer, bone metastases, post-menopause, diagnosis

Introduction

Vulvar cancer is a rare malignancy of the genital tract, representing the fourth most common type in this category, with a rate of

6% of all gynecological neoplasms [1]. Approximately 1,150 deaths from vulvar cancer are reported each year in the United States [1,2]. Vulvar neoplasia is known to be a disease of older women, but in recent years

there has been a growing prevalence among younger women [1,3].

The morphological variants of vulvar cancer are represented by squamous cell carcinomas with a percentage of over 90% of all types of vulvar cancer, while the others are represented by basal cell, keratinizing, warty and verrucous carcinomas [1,4].

Human papilloma virus (HPV) is a major risk factor for genital cancer, which can be associated with vulvar cancer in young women and can lead to a pre-invasive disease known as vulvar intraepithelial neoplasia (VIN). Also, in these cases, another risk factor is the history of cigarette smoking [3]. Cases of VIN associated with HPV have been reported rarely in the elderly and chronic vulvar dystrophy may be associated with these situations, but no strong correlation has been shown [3]. Although there are studies that show a better prognosis in HPV-positive tumors in vulvar cancer, there are still some inconsistencies [1]. In some recent studies, HPV infection was found in 3.3% of cases of vulvar neoplasia, while in other studies HPV infection had a prevalence of 76.5% of cases of this disease [5]. In previous reports, the risk factors associated with vulvar cancer were diabetes, obesity, or high blood pressure, but today they may reflect the fact that this neoplasm occurs in older women [6]. Because vulvar cancer seems to be more common in poor and elderly women in some regions, it has been hypothesized that inadequate hygiene and health care may be risk factors for vulvar neoplasia [3].

In terms of symptoms, the most common form of clinical presentation is long-term pruritus, a lump, or a mass on the vulva [7]. They occur in more than 50% of patients with invasive vulvar cancer, while in rare cases, the clinical presentation may be a small, warty or cauliflower-like growths lesion (Fig. 1,2). In all these cases or other suspicious lesions, a biopsy should be done. Vulvar neoplasia

occurs in about 70% of cases on the labia, especially on the labia majora [8].



Fig. 1 Advanced vulvar cancer, superior view (Department of Obstetrics and Gynecology, University Emergency Hospital Bucharest, Clinic's collection)



Fig. 2 Advanced vulvar cancer, local extension (Department of Obstetrics and Gynecology, University Emergency Hospital Bucharest, Clinic's collection)

Imaging examinations can be used to assess the stage of vulvar neoplasia, and MRI is one of the most appropriate methods because it can assess the local growth of vulvar cancer, lymphadenopathy, or distant metastases [9]. Despite all these possibilities, the safe diagnosis is established by histopathological

examination of the vulvar biopsy or surgical sample.

Despite its histological type, in most cases, invasive vulvar cancer metastasizes primarily through the lymphatic system [10].

The Department of Obstetrics and Gynecology of University Emergency Hospital Bucharest, the largest multidisciplinary medical unit in Romania, started on January 1, 2015, the study "Diagnosis and complex strategies treatment in gynecological cancers" (22280/ 21.04.2021), with the approval of the Local Ethics Committee of Bucharest University Emergency Hospital. The national, single-center, investigational, retrospective, and prospective study aimed to analyze the management compliance and positive diagnosis rate. As observational in recent years, the clinic has faced an increasing incidence of surgically obsolete gynecologic cancer cases.

Specific bone-metastases pattern

Gynecological malignancies, a category that includes ovarian, uterine, cervical, vulvar, and vaginal cancers, affect a huge number of women of all ages around the world [11]. Vulvar cancer has the lymphatic pathway to spread, rather than the hematogenous pathway. Bone metastases related to gynecological cancers are rare, often underdiagnosed, and have a very poor prognosis [12]. Bone metastases are common in hematogenous tumors, such as prostate and breast cancer, as the bones have a high blood flow in the red marrow, a high production of angiogenic factors that stimulate tumor growth, and there are tumor adhesive molecules that promote the binding to the bone marrow stromal cells. The most common site of metastasis in vulvar cancer is the lung, which is affected in about 45%, followed closely by the liver and the brain [13]. According to published reports, bone metastases are present in about 10% to a

quarter of cases, and the most common affected sites are the spine, pelvic bone, ribs, skull, limb bones and sternum [14] (Fig. 3).

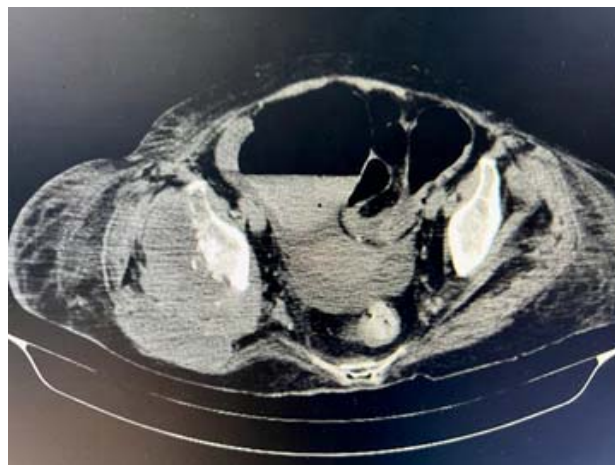


Fig. 3 CT image. Acetabulum osteolytic metastasis in a 73-year-old female, secondary to vulvar adenocarcinoma

In this context, the staging protocol includes mandatory chest X-ray and liver ultrasound; bone scan is recommended only in selected cases with specific symptomatology, so the possibility of missed cases and a much higher real incidence are very likely [15]. Expressed in this way, such cases do not seem exceptional. However, given that vulvar cancer has an incidence of about 1/ 100,000 women per year, according to the data mentioned above, the incidence of vulvar cancer with bone metastases is estimated to be one in one million women per year.

In patients with vulvar cancer complicated by bone metastases, pain is the main directive symptom and imagistic investigations such as Computed Tomography/ Positron emission tomography (CT/ PET-CT), Magnetic resonance imaging (MRI) and X-ray may clarify the diagnosis by identifying a stromal reaction rather than the cancer foci [16].

Two types of bone metastases are described: osteolytic, characterized by bone destruction, and osteoblastic, described as sclerotic, with bone formation. Bone metastases from gynecologic cancer are predominantly osteolytic [17]. This is a multi-

step process that occurs late in the disease progression and includes, firstly, the detachment of tumor cells from the primary tumor and the invasion of the blood vessels; secondly, the attraction and adherence to the endosteal surface and subsequently, the bone colonization. Osteolytic lesions are most common in multiple myeloma and breast cancer and are caused by the stimulation of osteoclast differentiation under tumor impulses [18].

Bone metastases lead to skeletal-related events. These are complications that include, in addition to bone pain, pathological fractures, spinal bone compression and fractures and hypercalcemia [19]. Most of the published studies on the appropriate treatment for vulvar cancer complicated by bone metastases report radiotherapy, chemotherapy, and surgery as first line therapies. But, once diagnosed, such cases require a multidisciplinary approach given their complexity. Bisphosphonates, such as zoledronic acid, alendronate, risedronate, ibandronate or denosumab can be effectively used for relieving the associated pain and for reducing the spinal cord compression and fractures [20].

The aim of the case report was to highlight the importance of active and multidisciplinary management of cases of vulvar cancer, the result being that patients could obtain a satisfactory quality of life.

Conclusion

The bone microenvironment has as a unique feature, the high sensitivity to the endocrine status. So, as vulvar cancer affects postmenopausal women, with a mean age of 70 years, it is mandatory to mention the theory regarding the protective role of estrogen on bone density and common factors identified in bone metastases and estrogen deficiency like impaired monocyte and

macrophage functions with impaired immunity and imbalance between pro-inflammatory and anti-inflammatory factors. This theory remains an open door for future protection strategies against bone metastases and treatment, because once it occurs, this complication is associated with a bleak prognosis of the case.

Conflict of Interest statement

Authors declare no conflict of interest.

Informed Consent and Human and Animal Rights statement

Informed consent has been obtained from all individuals included in this study.

Authorization for the use of human subjects

Ethical approval: The research related to human use complies with all the relevant national regulations, institutional policies, is in accordance with the tenets of the Helsinki Declaration, and has been approved by the review board of University Emergency Hospital Bucharest, Bucharest, Romania.

Acknowledgements

None.

Sources of Funding

None.

Disclosures

None.

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