REVIEW

HPV Infection and Vulvar Cancer

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Abstract

Vulvar cancer is an uncommon gynecological malignancy primarily affecting postmenopausal women and is the fourth most common gynecologic cancer. There is no specific screening and the most effective strategy to reduce vulvar cancer incidence is the opportune treatment of predisposing and preneoplastic lesions associated with its development. Vulvar carcinoma can be HPV-positive or HPV- negative. Any suspicious vulvar lesion should be biopsied to exclude invasion.

Key words: HPV, infection, vulvar cancer.

Introduction

HPV infection plays a central role in the development of vulvar cancer, HPV 16 and 18 are the most frequently reported genotypes that might induce this kind of lesions. It has been demonstrated that HPV infection plays a central role in the development of other malignancies such as vulvar, vaginal or anal cancer in women and anal or penile cancer in men [1]. Squamous cell carcinoma (SCC) of the vulva, the most common subtype, has traditionally been regarded as a disease of postmenopausal women, although the mean age of incidence has fallen in recent years owing to the increase in HPV infections worldwide [2, 3]. Squamous cell carcinomas represent more than 90% of all vulvar cancer and are associated with several histopathological subtypes such as keratinized, basaloid warty or verrucous lesions [4]. The high-risk HPV types 16,

31 and 33 are frequently detected in vulva cancer and its precursor lesions (VIN). Vulva cancer with basaloid histopathology in young women is often associated with HPV-69 [1, 5, 6, 7].

Diagnosis

Any suspicious vulvar lesion should be biopsied to exclude invasion. This can be done under local anesthetic with a 3 or 4 mm Keyes biopsy instrument, or with an incisional or wedge biopsy. Even if the lesion is small, it is better not to excise the entire lesion at the time of biopsy, as this makes the subsequent definitive surgery difficult to plan [8].

Risk factors

Risk factors for vulvar cancer include smoking, vulvar dystrophy, HPV infection, a history of high-grade CIN, VIN, and immunodeficiency syndromes (HIV infection) [9, 10]. The rate of VIN progression to invasive vulvar carcinoma is low [11, 12]. Definitive surgery is the first treatment for early-stage vulvar cancer [13, 14]. The studies indicated that the use of condom and really circumcision reduces the risk of HPV infections, and subsequently CIN and VIN in women andpenile lesions in men [15, 16].

Cigarette smoking was found to increase the risk of CIN3 and cervical cancer among women infected with oncogenic HPVs as compared to women who do not smoke. A synergistic effect was reported between cigarette smoking and HPV16 DNA load for development of cervical cancer in Sweden women [17]. The impact of cigarette smoking has focused on humoral immune responses to HPV and on the prevalence, incidence, and persistence of HPV infections [17]. A recent in vitro study demonstrated that exposure of cervical cells to Benzoapyrene, a major carcinogen in cigarette smoke, stimulates higher levels of virion synthesis in HPV-infected cells. On the other hand, the researchers showed that among smokers, the viral load did not change significantly by the intensity and duration of cigarette smoking, suggesting a low threshold for the effect of smoke on HPV DNA load [17].

Symptoms

While vulvar cancer may be asymptomatic, most women present with vulvar pruritus or pain, or have noticed a lump or ulcer. They may also have abnormal bleeding or discharge, and many will have a history of vulvar symptoms due to underlying lichen sclerosis or HSIL. Advanced vulvar cancer may present with a lump in the groin due to lymph node metastases [8].

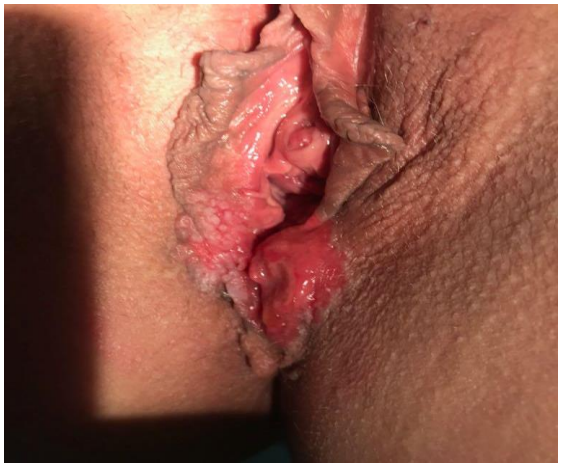

Fig.1: Invasive vulvar squamous cellcarcinoma with HPV 16 infection

(Personal archive Dr. Florica Șandru)

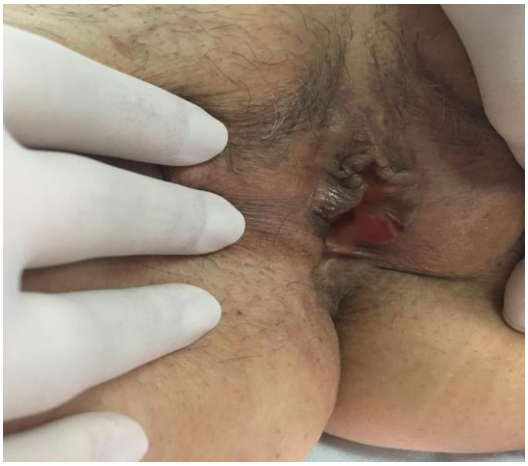

Fig. 2: Vulvar intraepithelial neoplastic lesion stage III

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Investigations

1. Cervical cytology, and colposcopy of the cervix and vagina, if applicable, due to the association of HPV-related cancers with other squamous intraepithelial lesions [18]. Full blood count, HIV testing, biochemical profile, liver profile [18].
2. Chest X-ray [18].
3. CT or MRI scan of the pelvis and groins may be helpful, especially for locally advanced tumors, to detect any enlarged lymph nodes in the groins or pelvis, erosion into underlying bone, or other metastases [19]. In addition, CT or MRI could be useful in further treatment planning.
4. ^{18}F fluorodeoxyglucose (^{18}F-FDG) positron emission tomography with computed tomography (PET-CT) can more effectively assess and detect inguinofemoral lymph node involvement compared with CT, influencing the planning of primary surgery and inguinal lymph node dissection to determine the optimum surgical extent without sentinel lymph node dissection and use of frozen sections [19]. Additionally, PET-CT might be used with larger tumors when metastatic disease is suspected or in the recurrence scenario [20].

Histopathological types

Squamous cell carcinomas (SCC) account for the vast majority of vulvar cancers (more than 80%), and melanomas are the next most common cancer. Rarer histological types include:

1.Basal cell carcinoma
2. Verrucouscarcinoma
3. Paget's disease of the vulva
4. Adenocarcinoma,not otherwise specified
5. Bartholin gland carcinoma [18]

Histological grades

1. GX: Grade cannot be assessed
2. G1:Well differentiated
3. G2:Moderately differentiated
4. G3:Poorly or undifferentiated [18]

Treatment

The treatment of vulvar cancer depends primarily on histology and staging. Other variables influencing management are age, coexistence of comorbidities, and performance status of the patient. Treatment is predominantly surgical, particularly for SCC, although concurrent chemo-radiation is an effective alternative, particularly for advanced tumors, and those where exenteration would be necessary to achieve adequate surgical margins [21]. Management should be individualized, and carried out by a multidisciplinary team in a cancer center experienced in the treatment of these tumors [22,23]. Other therapies such as chemotherapy and immunotherapies are usually reserved for metastatic or palliative settings, or for the treatment of rare diseases such as melanoma [23-26].

Conclusions

HPV infection has a central role in developing premalignant or malignant vulvar lesions. Patients diagnosed with HPV-related lesions tend to have a younger age at diagnosis, especially due to the

association with the presence of this virus. When it comes to the prevention of these lesions, it seems that anti-HPV vaccination might play a role.

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