Metachronous squamous neoplasias of the cervix and vulva

Neoplazii metacrone scuamoase la nivelul cervixului și al vulvei

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Abstract

We describe the case of a patient with invasive cervical carcinoma, irradiated and operated according to protocols, who was later operated for invasive vulvar carcinoma. Simple, moderate, severe vulvar dysplasia (VIN III) and areas of invasive squamous vulvar carcinoma were discovered on pathology suggesting that the vulvar lesion occurred and evolved locally, as a primary vulvar lesion, and not as a vulvar spread of the previous cervical carcinoma. Additionally, the slow evolution rate of the vulvar lesion seems incompatible with the evolution of a metastasis from a distant carcinoma. Although high risk HPV infections is accepted as a common etiology for cervical and vulvar neoplasms, the pathogenesis of metachronous squamous lesions on the cervix and vulva is unclear, especially at genomic level and the debate, as to whether multicentric CIN 3/carcinoma in situ/invasive carcinoma lesions arise independently, de novo at different sites, or share a monoclonal origin, is still continuing.

Keywords: *metachronous squamous lesions, clonal origin, cervix, vulva*

Rezumat

Lucrarea descrie cazul unei paciente cu carcinom cervical invaziv, iradiata și operată conform protocoalelor (2004), care ulterior a dezvoltat carcinom vulvar invaziv (2007). Neoplazia vulvară a fost biopsiată repetat, în final practicându-se vulvectomie totală cu limfadenectomie inghinală bilaterală (2015). Examenul histopatologic al leziunii vulvare a decelat displazie vulvară simplă, moderată și severă, precum și arii de carcinom vulvar invaziv, sugerând că originea primară vulvară a leziunii, și nu secundară carcinomului cervical invaziv, tratat anterior. Evoluția locală lentă a leziunii pare, de asemenea, incompatibilă cu evoluția unei metastaze la distanță pornită de la un carcinom cervical invaziv. Deși este acceptată implicarea HPV cu risc înalt ca factor etiologic comun pentru carcinomul cervical și vulvar, patogeneza leziunilor scuamoase metacrone ale colului și vulvei nu este elucidată, în special la nivel genomic, existând întrebarea dacă leziunile multiple de tip CIN/VIN I, II, III sau invazive apar independent, de novo, sau au origine monoclonală.

Cuvinte-cheie: *leziuni scuamoase metacrone, origine clonală, col, vulvă*

Introduction

Many studies showed that prior history of cervical carcinoma, either *in situ* or invasive, is a risk factor for the development of vulvar cancers[1,2]. There are three explanations for this association: 1 - women with cervical neoplasia frequently are infected with HR-HPV both at the cervix and at the vulva and they develop a independent neoplasma at these two sites, 2 - subsequent vulvar carcinoma occur as a recurrence of the original cervical cancer after hysterectomy, and 3 - development of a second primary neoplasm in the vulva as a result of radiation therapy for the prior cervical neoplasm[3].

Case presentation

We describe a case of invasive cervical carcinoma, irradiated and operated according to protocols, that was later operated for invasive vulvar carcinoma.

The patient, a 58-year-old female, was diagnosticated with *in situ* cervical carcinoma on cervical biopsy, in 2004. Hysterectomy was performed, and pathology revealed at cervical level *in situ* cervical carcinoma with islets of invasive squamous cervical carcinoma. Surgery was followed by chemo- and radiation therapy.

In 2007, on regular examination, the patient accused vulvar pruritus and a vulvar lesion was discovered and biopsied: moderate and severe vulvar dysplasia (VIN II and VIN III) and small foci of microinvasive squamous carcinoma. The patient refused local excision. The lesion evolved, and in 2015, the patient presented with extensive lesion of vulva, from urethra to anus.

Exfoliative cytology (in 2015) from vulvar and perianal lesions was HSIL, and cytology from vaginal stump was normal. HPV genotyping was positive for HPV types 16 and 55. Preoperative multiple site biopsies were performed, revealing severe vulvar dysplasia VIN III. Simple vulvectomy was performed and pathology revealed simple, moderate, severe vulvar dysplasia (VIN III) and areas of invasive squamous vulvar carcinoma. Figure 2 is presenting the summary of the clinical histories of the patient no. 6 from Vinokurova et al.[4] study and from our patient, with cervical and vulvar metachronous lesions.

Although not done at time of cervical carcinoma diagnosis, HPV genotyping was performed before vulvectomy and it was positive for HPV types 16 and 55. Our opinion is that the presence of simple, moderate and severe vulvar dysplasia, together with areas of

invasive squamous vulvar carcinoma, on pathology specimen suggest that the vulvar lesion occurred and evolved locally, as a primary vulvar lesion (HPV determined), and not as a vulvar spread of the previous cervical carcinoma. Additionally, the slow evolution rate of the vulvar lesion seems incompatible with the evolution of a metastasis from a distant carcinoma.

Discusions

Most of invasive squamous cell carcinomas in the cervix, vagina, and vulva are occuring in patients with persistent high risk HPV infections at these sites[5-7].

However, compared with cervical cancer, vaginal and vulvar cancers occur more rarely (current age-adjusted incidences of cervical, vaginal, and vulvar cancers are, respectively, 8.9/100 000 women per year, 0.7/100 000 women per year, and 2.3/100 000 women per year)[8].

Although high risk HPV infections is accepted as a common etiology for cervical and vulvar neoplasms, the pathogenesis of metachronous squamous lesions on the cervix and vulva is unclear, especially at genomic level. There is a debate as to whether multicentric CIN 3/carcinoma *in situ*/invasive carcinoma lesions arise independently, *de novo* at different sites, or share a monoclonal origin[9,10].

Supporting the monoclonal origin of metachronous multicentric cervical and vulvar lesions, the study of Vinokurova et al.[4] investigated the clonality of multicentric carcinoms and high-grade squamous intraepithelial lesions located on the cervix, vagina, and vulva. Of the seven cases included, one case presented with invasive cervical carcinoma with metachronous vulvar carcinoma. The same sequences of specific HPV DNA integration sites (case 6 - 14q32) were present in both cervical and vulvar lesions, suggesting that both lesions share the same monoclonal origin. The monoclonal origin of both lesions implies a way through which cervical neoplastic cells migrate to the vulva, which is still unknown. Vinokurova et al. supposed that these

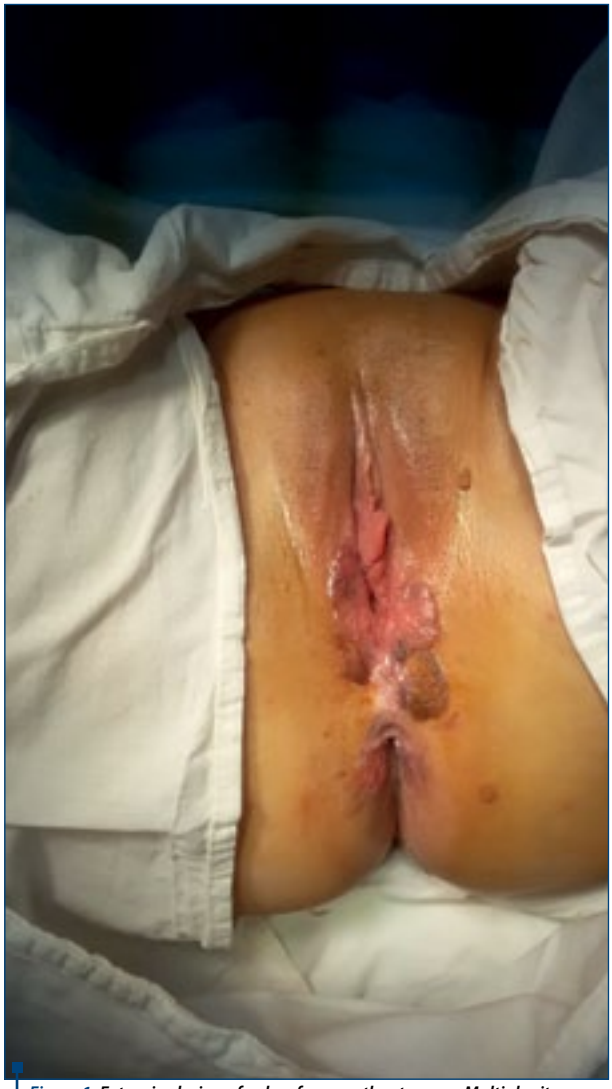

Figure 1. Extensive lesion of vulva, from urethra to anus. Multiple sites biopsies were performed

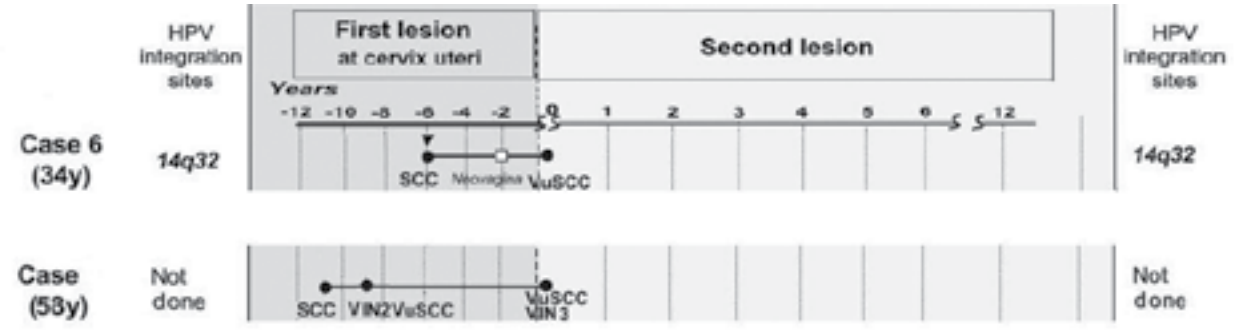

Figure 2. The summary of the clinical histories of the patient no. 6 from Vinokurova et al. study and from our patient (58 y), with cervical and vulvar metachronous lesions (adapted from Vinokurova et al.[4])

vulvar neoplasias arised from dormant dysplastic HPV transformed cells, disseminated early during carcinogenesis. For the moment, these cells are undetectable by conventional cytology and histopathology.

Conclusions

Prior cervical carcinoma can be associated the late metachronous vulvar neoplasias. The mechanism of this association is still unknown. This should stress the importance of adequate follow-up of these patients, with thorough examination of vagina and vulva.

Macroscopic lesions should be promptly biopsied and adequate treatment offered to the patient.

For patients with prior cervical cancer and no lesions of vulva, indefinitely annual vaginal Pap screening should be offered, according to American College of Obstetricians and Gynecologists screening recommendations. ■

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