Review paper

Vulvar cancer in a patient with long-lasting premalignant lesions in the genital area: easily overlooked and difficult to diagnose – a case report and literature review

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Abstract

Vulvar intraepithelial lesions are a heterogenic group of diseases, which can be easily misdiagnosed. The case of a 61-year-old woman with a history of genital intraepithelial lesions and infection with HPV is presented. Her main complaint was vulvar pruritus. Vulvoscopy revealed the presence of two skin lesions: the first one had the morphology of lichen sclerosus, and the second of a Bowenoid lesion. The biopsy of the first lesion revealed vulvar intraepithelial neoplasia, whereas cells of squamous vulvar cancer were identified in the second lesion. After staging, the patient was advised to undergo hemivulvectomy and lymphadenectomy. The coexistence of morphologically diverse vulvar skin lesions may cause difficulties with diagnosis and the selection of an adequate treatment. Long-term follow-up and regular examination are essential for diagnosis of vulvar malignancies in the early stage.

Key words: Papillomaviridae, vulvar neoplasms, vulvar diseases, vulvar lichen sclerosus.

Introduction

Vulvar squamous cell carcinoma (SCC) is a rare type of malignant neoplasm, accounting for approximately 4% of all genital cancers in women with a substantial majority of vulvar malignant tumours occurring in post-menopausal women [1]. There has been a significant increase in the incidence of vulvar squamous intraepithelial lesions and vulvar cancer for the past 30 years, including the younger population [2, 3]. This trend may be explained by the growing number of HPV infections of the lower genital tract and more effective diagnostic procedures [2]. Clinicians have shown a considerable interest in identifying and preventing precancerous conditions, which has resulted in continuous improvement in the classification of vulvar lesions. The terminology of vulvar squamous intraepithelial lesions, published in 2015 by the International Society for the Study of Vulvovaginal Disease (ISSVD), recognizes the presence of HPV as a determining key for the classification of these disorders [4]. One form, HPV-positive

squamous intraepithelial lesion, includes vulvar low-grade intraepithelial lesion (LSIL) and vulvar high-grade intraepithelial lesion (HSIL), previously known as vulvar intraepithelial neoplasia usual type [4]. This form usually occurs as a multifocal Bowenoid lesion in post-menopausal women (aged 40–49) and is associated with a high-risk type of HPV (usually type 16, 18 and 33) [1, 3]. Thus, the risk factors remain similar to those leading to the development of cervical intraepithelial neoplasia and are directly linked to the HPV infection (i.e., multiple sexual partners, immunosuppression, tobacco use) [1, 5]. HPV-positive vulvar squamous intraepithelial neoplasia develops into invasive cancer in approximately 6% of cases (basaloid/warty SCC) [1].

In contrast, a HPV-negative vulvar precancerous lesion (VIN differentiated type) appears to be considerably different in its aetiology, risk factors, mean age of patients at diagnosis and progression rate to invasive cancer. Usually, older women (aged 66–69) are affected [1]. The frequency

of progression to invasive cancer is nearly six times higher for VIN differentiated type compared to HSIL [1].

Any suspected vulvar lesion should be biopsied by punch or incision biopsy, and the specimen should be evaluated by an experienced pathologist. Lymph node examination remains an indispensable part of staging and has a significant influence on the patient's prognosis. Surgery is the treatment of choice of vulvar cancer [4, 6, 7]. Primary surgery may be supplemented with radiation or/and chemotherapy, depending on the lesion's pathology and staging [7].

We report the case of a patient with vulvar squamous intraepithelial lesions of diverse morphology, history of vaginal and cervical premalignant lesions as well as an infection with HPV type 53 (high risk) [8–11]. The histological examination confirmed the presence of preinvasive cancer. The HPV DNA test of the postoperative tissue was positive for type 16 (high risk).

Case report

In March 2017 a 61-year-old woman with diabetes mellitus, hypertension, and tobacco use was admitted to a tertiary care centre due to vulvar pruritus, which had developed approximately 3 months before a routine follow-up visit, during which the symptom was reported.

The patient had been diagnosed with cervical leukoplakia 26 years earlier and treated with conisation. The specimen examination revealed cervical intraepithelial neoplasia grade 2 (CIN 2). Thirteen years later, the patient had been diagnosed with CIN 2 for the second time along with vaginal intraepithelial neoplasia grade 2 (VaIN 2) and vulvar intraepithelial neoplasia grade 2 (VIN 2). All lesions were removed with cold knife. In the same year, the specimens from the cervix and vulva were tested for HPV DNA and were both positive for HPV type 53.

Because of the patient's main complaint, vulvoscopy was conducted and revealed two suspicious lesions (both smaller than 10 mm in diameter) located lateral to the right labia minora and close to the posterior commissure (Figure 1). Both lesions were biopsied. The histological examination of the specimen with Bowenoid morphology revealed squamous cell carcinoma G1 – well differentiated, whereas the second specimen, exhibiting features typical for lichen sclerosus, was assessed as VIN 2. Inguinal lymph nodes were not palpable. Complementary evaluation of the cervix, vagina and anus did not reveal any pathological changes.

The patient was advised to undergo local excision with bilateral inguinofemoral lymphadenectomy (Figures 2 A–C), which was performed 2 months after the primary diagnosis. On each side of the lesion, at

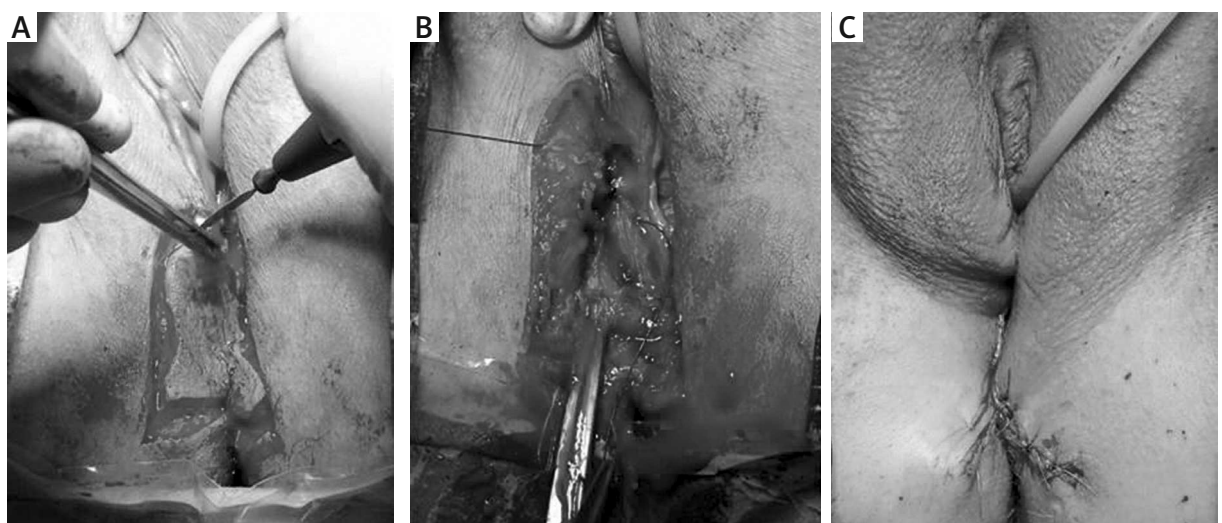**Figure 1.** Two lesions located laterally to the right labia minora

Figure 2. Hemivulvectomy. **A** – Primary incision. **B** – Operating field after removal of the affected flap. **C** – Postoperative view

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least six lymph nodes were removed. The postoperative histological assessment confirmed the presence of squamous cell carcinoma *in situ* and no nodal metastasis: 0/7 on the left side, 0/6 on the right side, lymph node ratio (LNR) = 0% (TNM pTis N0, Stage 0). The removed tissue was tested for HPV DNA and was positive for HPV type 16.

On day 10 after surgery, the patient was discharged, but a wound infection developed 7 days later. It was treated by opening the wound and Aqua-Gel® dressing (KIKGEL, Ujazd, Poland) for 10 days. No further complications were observed in the subsequent 6-week follow-up period.

The clinicopathological findings were assessed based on the TNM criteria for vulvar cancer unless otherwise stated [6].

Discussion

The presented case confirms that the natural history of vulvar cancer is complex and can be influenced by various factors. The current literature indicates that the percentage of vulvar cancer caused by HPV infection ranges between 30% and 69% [7, 12–14]. The most widespread HPV high-risk types (not only type 16 but also 18, 31 and 33) are associated with vulvar cancer in 14–60% of cases [15]. This fact stands in contrast to squamous cell carcinoma of the cervix, where the prevalence of HPV is nearly 100% for invasive disease [15].

Biological and epidemiological evidence of the oncogenic potential of HPV type 53 is based on studies concerning cervical cancer [8–11]. However, the association of HPV type 53 with vulvar cancer has remained a controversial issue [16, 17]. Despite the presence of HPV type 16 in the removed tissues, one cannot exclude the role of HPV type 53 in the development of vulvar cancer *in situ* as well as cervical and vaginal premalignant lesions in the past medical history.

HPV-positive precancerous lesions often coexist with other precancerous conditions of the lower genital tract. Women with SCC developed from vulvar HSIL are more often diagnosed with high-grade squamous intraepithelial lesion of the cervix (cervical HSIL) compared to women with differentiated VIN related SCC (35% vs. 2%) [18]. As the presented case shows, the extended examination of this area may be not only recommended but necessary [6].

Other risk factors for vulvar cancer were also analysed. Heavy cigarette smoking is commonly mentioned in published studies as an established risk factor [1, 2, 5, 19]. Diabetes mellitus and hypertension may correlate in 25–40% of cases with the incidence of vulvar cancer but do not seem to be responsible for the development of this condition [20]. What is unusual about the described case is the coexistence of HPV-positive vulvar cancer *in situ* and lichen sclerosus, which can be diagnosed when the lesion meets the morphological criteria [21]. In the presented case, the whitish, hypertrophic lesion with hyperkeratosis

and loss of architecture leading to fusion in the midline between labia majora and minora meets the diagnostic requirements for lichen sclerosus (LS) (Figure 1).

LS is a type of skin inflammatory condition. Pruritus, which is characteristic for those diseases, is deemed to drive the 'itch-scratch cycle' and leads to hyperplasia, atypia, dysplasia and, eventually, invasive cancer (typically keratinizing SCC) [1, 20]. It cannot be excluded that the two proposed models of invasive vulvar cancer may be complementary in certain cases.

For the vulvar squamous intraepithelial lesions and preinvasive vulvar cancer, repeated biopsies remain an indispensable tool for early diagnosis. The Eastern Cooperative Oncology Group (ECOG) requires at a minimum the identification of the histological type and depth of invasion in the pathology report [6].

There are four main treatment modalities for vulvar HSIL when the occult invasion is not suspected – carbon dioxide laser vaporization, 5-aminolevulinic acid (ALA) photodynamic therapy, topical imiquimod and loop electrosurgical procedure (LEEP) [5, 21–23]. Widely discussed usage of imiquimod can be limited by side effects (mainly erythema and vulvar pain) and a high recurrence rate (30–50%) [25]. In case of cancer suspicion, excision with 0.5–1 cm margins remains the preferred initial intervention. There has been a gradual trend toward more conservative therapies of high-grade VIN – recently cidofovir has been shown to be effective, but more research is needed [22, 24].

While HPV vaccine in the primary prevention of HPV-associated premalignant genital lesions was proved to be effective, the role of the vaccine in the secondary prevention and treatment has not been fully established [2, 22, 25]. In previously seropositive women, HPV vaccine may augment the response by activating T-cells capable of eliminating infected cells, rather than initiating the production of antibodies against the virus itself [25]. The results from the studies assessing therapeutic vaccines targeting viral oncoproteins E6 and E7 in patients with premalignant genital lesions are promising, however its safety and efficacy should be studied before the introduction to the clinical practice [2, 25].

There are numerous management options for vulvar LS, whereas there is good evidence for topical corticosteroids (TCS) as the first-line treatment to achieve remission [22, 26]. The therapy should be individualized and the decision with which TCS to begin the treatment should be based on severity of hyperkeratosis and the symptoms [26]. In most cases the initial usage of ultrapotent/superpotent (e.g. clobetasol propionate or betamethasone dipropionate) is advised [22, 26]. Once the symptoms are supressed, a gradual reduction of TCS potency, carefully titrated to clinical outcome, should be attempted [26]. Regular check-ups and good compliance remain essential for achieving remission and reduction in the risk of malignant transformation. In the study of

Lee *et al.* cancer did not develop in any of the 357 compliant patients treated with TCS, while it occurred in 7 out of 150 (4.7%, $p < 0.001$) cases in the partially compliant group and the risk of developing malignancy was close to the risk in untreated women (5–6%) [26].

Other possible treatment options for vulvar LS include calcineurin inhibitors and systemic treatments (e.g. retinoid acitretin may be helpful in hypertrophic cases). In contrast, for any vulvar lesion derived from LS and suspected of intraneoplasia surgical cold knife excision remains a standard [21].

For the successful treatment of vulvar cancer, surgery remains essential [6, 7, 19, 20]. According to large cohort studies, the prognosis of patients with vulvar cancer depends mostly on the FIGO stage, LNR and histological grade [27, 28]. In the present case, the fact that both G1 and LNR = 0% is encouraging for the patient's survival. This result was most likely achieved due to regular follow-up visits due to the patient's complex past medical history related to HPV infection of the lower genital tract. This result also highlights the clinical value of long-term observation in this group of patients. Available publications lack consensus on any molecular profiling associated with the prognosis of recurrence risk [28].

Conclusions

The morphology of vulvar skin lesions often reflects their complex pathogenesis and sometimes combines major features of different established types. If the co-existence of an HPV-positive lesion and chronic skin inflammatory disease is diagnosed, it is necessary to consider their mutual interaction, including the possible increased risk of carcinogenesis. Long-term, regular follow-up remains essential for invasive cancer prevention and should include examination of the genital area. The testing of HPV high-risk types from the vulva specimen may be helpful in identifying the groups of patients particularly susceptible to developing cancer.

Conflict of interest

The authors declare no conflict of interest.

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