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Recurrent vulvar dysplasia after a prior carcinoma of the cervix: A case of field effect

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Abstract:

Vulvar intraepithelial neoplasia (VIN) is a dysplastic condition of the squamous epithelium of the vulva. There are two types of VIN: high-grade squamous intraepithelial lesion of the vulva and VIN differentiated type (dDVIN). Management includes excision, laser ablation, and topical therapy. An excisional procedure used in VIN is simple local excision and partial or total skinning vulvectomy. Despite treatment, its recurrence is high. A G5P5 (5004) woman in her 60s presented with vulvar pruritus and vulvar pain of 2 years. She was treated for cervical adenocarcinoma Stage IB1 with surgery and complete radiotherapy 27 years prior. She was diagnosed twice with vulvar dysplasia 12 and 21 years after the diagnosis of cervical malignancy, both times presenting as vulvar pruritus. She was subsequently managed with vulvectomy with bilateral groin node dissection and with wide local excision, respectively. A 3 cm × 2 cm well-circumscribed, irregular erythematous plaque at the introitus's 11–1 o'clock region was noted on physical examination. She was managed as a case of recurrent VIN III and underwent wide local excision and distal urethrectomy with split-thickness skin graft. The final histological examination of the submitted specimen showed human papillomavirus-associated classic VIN II.

Keywords:

Field effect, recurrent vulvar intraepithelial neoplasia, vulvar intraepithelial neoplasia

Introduction

Vulvar intraepithelial neoplasia (VIN) is a dysplastic condition of the squamous epithelium of the vulva. Despite treatment, 25% of cases recur. Here, we present a case of recurrent vulvar dysplasia in a patient previously diagnosed and treated for cervical cancer demonstrating the phenomenon of human papillomavirus (HPV)-associated field effect. Field effect has been previously reported in the literature to describe multiple premalignant and frankly malignant lesions in the oral cavity, breast, skin, and colon. However, literature describing field cancerization on the female genital tract is rare.

The case is presented to promote awareness that HPV infection could present with recurrent and multicentric lesions, in this case, initially infecting the cervix and then the vulvar area. Currently, there is no cure for HPV infection and the case highlighted the significance of HPV prevention and control to significantly reduce the burden of the disease.

Case Report

A G5P5 (5004) woman in her 60s presented with vulvar pruritus and vulvar pain of 2 years. She was otherwise well with no other constitutional symptoms. She has a known history of hypertension and diabetes. Pertinent to the sexual history of this patient include early coitarche at 13 years old and oral contraceptive use for 4 years. She was treated for cervical

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adenocarcinoma Stage IB1 with surgery and complete chemoradiotherapy 27 years prior for which physical examination, cytology, and yearly imaging showed no evidence of disease. She was diagnosed twice with vulvar dysplasia 12 and 21 years after the diagnosis of cervical malignancy, both times presenting as vulvar pruritus. This was histopathologically proven and subsequently managed with vulvectomy with bilateral groin node dissection and with wide local excision, respectively. Pelvic examination revealed a hypopigmented bilateral labia, with a 3 cm × 2 cm well-circumscribed, irregular erythematous plaque at the 11–1 o'clock region of the introitus, the vagina was smooth, intact vaginal stump, with a note of a 2 cm × 2 cm posterior vaginal wall, bilateral paracolpia smooth, and pliable [Figure 1]. Metastatic workup was negative. Keyes punch biopsy of the mass showed VIN III and she subsequently underwent wide local excision and distal urethrectomy with split-thickness skin graft [Figure 2]. Upon wide local excision, a vulvar specimen was obtained measuring 7 cm × 5 cm × 1 cm. There was a 2-cm margin excised around the lesion and 1-cm margin in the area toward the urethra. The specimen was excised 1 cm deep into the subcutaneous tissue. On the cut section of the lesion, it had no signs of gross invasion. A 1 cm × 1 cm × 0.5 cm urethra was excised *en bloc* with the specimen and was grossly free of any lesions. Histological examination of the submitted specimen showed HPV-associated classic VIN II [Figure 3].

Postoperatively, the patient was followed up every other week until the postoperative site showed good uptake of graft and healing and then every 6 months after that. A recent vulvar examination showed a completely healed postoperative site, no vulvar masses seen, and internal examination revealed a smooth, intact vaginal bilateral paracolpia smooth, and pliable.

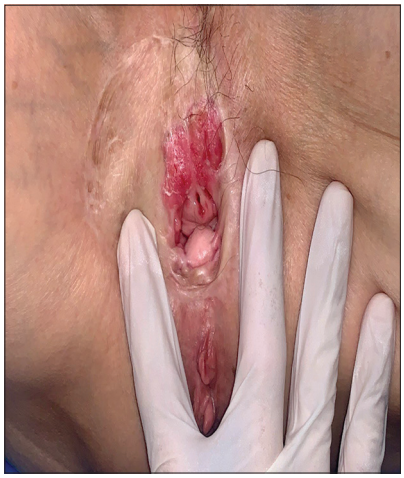

Figure 1: A 3 cm × 2 cm well-circumscribed, irregular erythematous plaque at the 11–1 o'clock region of the introitus was seen during the pelvic examination

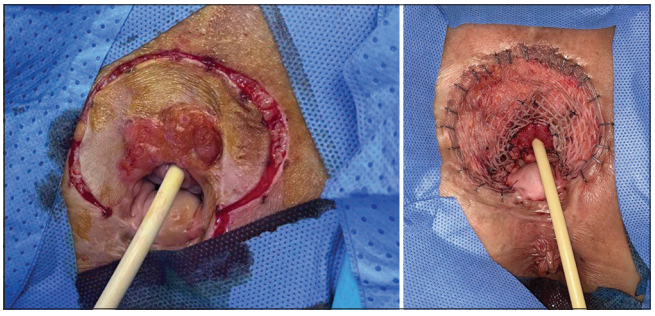

Figure 2: Wide local excision, distal urethrectomy with split-thickness skin graft was performed in this patient

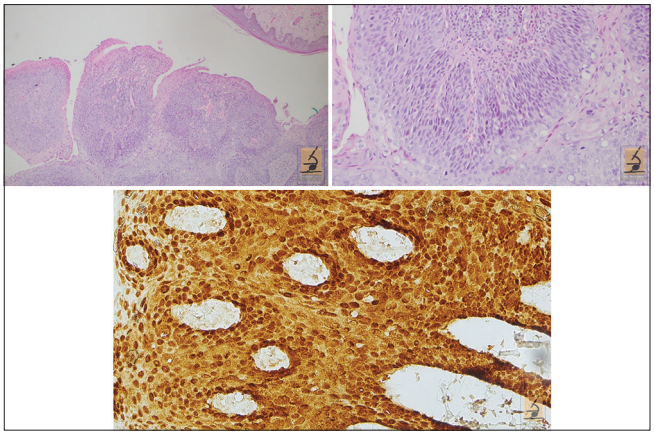

Figure 3: Pictomicrograph of submitted specimen showing classic vulvar intraepithelial Neoplasia II with p16 staining

Discussion

VIN is a dysplastic condition of the squamous epithelium of the vulva. It is a premalignant lesion and precursor of vulvar carcinoma. There are two distinct premalignant types of VIN: high-grade squamous intraepithelial lesion (HSIL) of the vulva and VIN differentiated type (dVIN).[1] HSIL of the vulva, also known as VIN usual type (uVIN), is more common in young women, with peak prevalence at age 25 years or less, and is associated with HPV. uVIN tends to be multifocal and multicentric. Smoking, number of sexual partners, immunosuppression, previous treatment of vulvar HSIL, and a history of HSIL of the cervix or vagina are all risk factors for HSIL of the vulva. VIN differentiated type (dVIN), on the other hand, is more common in older women. It is also seen in the setting of lichen sclerosus or planus. Compared to vulvar HSIL, it tends to be unifocal and unicentric. At the time of excision for VIN, occult invasive cancer is seen in 3.2. The rate of progression to vulvar cancer in 10 years is 10% for HSIL, whereas 50% in dVIN.[2]

About 20%–30% of VIN recur despite treatment. Risk factors for the development of the disease have already been elucidated. However, literature discussing the risks for recurrence is much more limited.

In a study by Satmary *et al*., 26.3% of VIN recur in 650 patients in a median follow-up time of 89 months. The median time to recurrence was noted to be at 16.9 months. At 43 months, 75% recurred. Furthermore, age >50, immunosuppression, metachronous vaginal or cervical intraepithelial neoplasia (CIN), positive excision margins, and adjacent lichen sclerosus or HPV were identified in this study as independent risk factors for recurrence. Regardless of treatment modality, 25% recurred.[3]

The recent increase in VIN incidence has been seen in younger women, however, for recurrence, an age >50 years was a significant risk. In the presented case, her first diagnosis of VIN and subsequent recurrences were noted when she was more than 50 years old which is consistent with previous studies. The increased propensity of recurrent VIN in this age group could be attributed to immunosenescence and its age-related changes in the immune system, but by no means that the older aged population are immunocompromised.

HIV infection and immunosuppression secondary to immunosuppressant use were cited as risk factors for recurrence. In a study by Bradbury *et al*., recurrence for HIV-positive women was 125.4/1000 persons-year (95% confidence interval [CI]: 74.3–198.1), whereas that of HIV-negative women this was 91.7/1000 persons-year (95% CI: 54.3–145).[4] RFS and PFS are shorter in HIV-positive women compared to HIV-negative women. Multifocal and multicentric disease is the norm for these women. On the other hand, immunosuppressive medication use, either due to this use or due to the underlying disease warranting its use, studies found a 2-fold increased risk for recurrence. The immunocompromised state of this group of patients results in failure to clear HPV infection and allows its persistence. However, HIV testing of this patient yielded negative results and the patient is not taking any form of immunosuppressive medications. This case exhibited that, in terms of VIN recurrence, an immunocompromised state is not necessary for VIN recurrence and immunocompetent patients must be followed up just the same.

Various studies found a significantly increased risk of recurrence with positive excision margins. In one study, VIN III was diagnosed in 73 women with vulvar biopsy and all were treated with surgical excision. Occult squamous vulvar cancer was seen in 22% at the initial surgical resection. Patients were examined postoperatively, and recurrence was confirmed when a biopsy of suspicious lesions confirmed VIN III. Of these, 39 (66%) had positive surgical margins, 18 (31%) had negative margins, and 2 (3%) had unknown margins. Recurrence was observed in 46% with positive surgical margins and 17% with negative surgical margins.[5] Furthermore, patients with positive margins have a shorter median time to recurrence. However, both groups maintained a persistent long-term risk of recurrence regardless of margin status.[3] As in this case, despite negative margins, multiple recurrences of VIN occurred. Even in positive margins, immediate re-excision is not recommended since it is not yet fully elucidated that this would ultimately improve the outcome. Furthermore, wound breakdown is a risk and there is a resultant undesirable anatomic alteration brought about by multiple re-excisions. For both cases, as long as there is no carcinoma and no visible residual disease, at the first sign of reoccurrence of disease, treatment options may include laser or topical medical therapy depending on disease location and extent, and the possibility for invasive carcinoma.

Recurrence is also associated with vaginal or CIN. A retrospective cohort study of women with a histologic diagnosis of VIN found significant associations between recurrence and metachronous vaginal intraepithelial neoplasia or CIN diagnosis with an odds ratio of 1.765 (95% CI = 1.084–2.875).[3] Furthermore, previous studies reported 10%–25% of patients with VAIN having metasynchronous VIN.[6]

The multiple recurrences in this case can be explained by a phenomenon called field effect. Also called, field defect or field cancerization, it is a premalignant phenomenon that is frequently attributable to HPV infection. It was originally described by Slaughter in 1953 to describe multiple primary oral squamous cell carcinomas and explain their local recurrence. Gynecologically, field effect refers to the involvement of different sites, such as the cervix, vagina, vulva, and anus, with multifocal disease. These lesions may occur synchronously or metachronously. This explains the multicentricity and multifocality of HPV-associated lesions. Support of this phenomenon relied on pathological examination, before the advent of molecular pathology. Because of the field effect, there is an inherent predisposition of normal-appearing cells to malignant transformation. However, cancer development, *per se*, is not a requirement for defining field effects.

The exact underlying mechanisms of the field effect in cancer are not fully understood. There are three possible theories that may explain this phenomenon: monoclonal spreading, persistent HPV infection, and infection of different HPV subtypes.[7]

In the theory of monoclonal spreading, a single clonal cell undergoes genetic transformation. This genetic transformation may range from benign to premalignant to malignant. This explains the multifocality and multicentricity of these lesions. The patient has been previously diagnosed and managed with cervical cancer. Even without the benefit of a p16 staining on

the previous hysterectomy specimen, the association of cervical cancer and persistent oncogenic HPV infection has long been established for which HPV 16 and 18 are the most common. The histologic type of cervical cancer in this case was adenocarcinoma. Despite the lesser degree of association of adenocarcinoma with HPV infection compared to its squamous cell carcinoma counterpart, HPV infection still accounts for most of the cases, accounting for 89%.[8] This genetic transformation in cells "spreads" to the same organ (multifocality) or adjacent organs (multicentricity) and induces lesions that can be both benign or malignant. In the case presented, a genetic transformation that initially induced the cervical malignancy may have also induced changes in the vulvar cells that brought about the dysplastic changes.

Second, the persistence of high-risk HPV infection may also explain field cancerization. The recurrent lesions described in this case may not be necessarily recurrent, but rather the persistence of the etiologic agent. The excision of the primary lesion may not necessarily remove the etiologic agent and the patient may still harbor the etiologic agent. Hysterectomy for cervical cancer in our patient and the subsequent multiple excision of the vulvar dysplastic lesions did not remove the HPV infection, rendering the patient susceptible to HPV-related extracervical lesions.

Third, several different HPV types may infect synchronously resulting to multiple different lesions. In one retrospective case–control study that determined the HPV genotypes present in multicentric lesions of the cervix, vagina, and vulva, multiple HPV genotypes were identified in 36.5% of the study population. HPV16 was the most common genotype. This is followed by HPV53 (24, 13.6%), HPV58 (22, 12.4%), HPV52 (19, 10.7%), HPV51 (17, 9.6%), HPV56 (17, 9.6%), and HPV18 (16, 9.0%).[9] In the case presented, infection of different genotypes of HPV cannot be proven since immunohistochemistries were not performed in the previous hysterectomy and the previous vulvar excision specimens.

Recently, the concept of field effect has expanded to include the effect of various etiologic factors. This is called the etiologic field effect. The etiologic factors include dietary, lifestyle, environmental, microbial, hormonal, and genetic factors, and their interactions among themselves contribute to a tissue microenvironmental milieu that constitutes a "field of susceptibility" to neoplasia initiation, evolution, and progression. The concept is cognizant of the importance of the interplay between diverse etiologic exposures in carcinogenesis. In this phenomenon, the etiologic field is defined as" a functional field of altered tissue microenvironment that is predisposed to the acquisition of somatic molecular changes through alterations in cellular and extracellular interactomes". If the field effect is characterized by cellular molecular changes, the etiologic field, on the other hand, is characterized by the presence of common etiologic exposures. Etiologic fields are not restricted to contiguous epithelial structures. Furthermore, etiologic exposures happened before cellular and molecular aberrations inducing a neoplastic initiation and progression. Thus"etiologic field effects" are potentially reversible and represent modifiable targets for intervention in the future.[10]

This case exhibited that HPV-associated lesions can be recurrent and it can occur after many years after the initial diagnosis even without the usual risk factors. Furthermore, it can be multifocal and multicentric, involving different nearby organs, owing to the phenomenon of field effect. It is important to diagnose these preinvasive lesions and precursors before they transform into frank vulvar malignancy.

A comprehensive diagnosis of multicentric lesions can be challenging, especially if it involves the vagina, vulva, or anal area, since these areas are easily missed on a clinical gynecologic examination. Furthermore, presenting symptoms of early preinvasive lesions in these areas are nonspecific, adding to the burden of their late diagnosis. Therefore, clinicians should be aware that a patient with HPV infection could present with multicentric lesions, and thereby a thorough gynecologic examination of the vulva, vagina, and anal area should be performed in patients with known HPV infection.

HPV infection could present with recurrent and multicentric lesions, in this case, initially infecting the cervix and then the vulvar area. Currently, however, there is no cure for HPV infection and this highlights the significance of HPV prevention and control. Access to affordable HPV vaccines will prevent and control HPV infection and transmission. On the other hand, access to appropriate and effective screening tests and management of HPV-infected will significantly reduce the burden of the disease. Together, these are the weapons against HPV infection and its resultant disease.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form, the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

Authorship contributions

Jessa Karyl R. Apa, MD - Involved in the conceptualization, formal analysis, provision of resources, data curation,

writing the original draft, reviewing and editing drafts, and visualization.

Jericho Thaddeus P. Luna, MD - Involved in the conceptualization, formal analysis, provision of resources, data curation, reviewing and editing drafts, and supervision.

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Conflicts of interest
There are no conflicts of interest.

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