Vulvar intraepithelial neoplasia

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Vulvar intraepithelial neoplasia (VIN) is a high-grade intraepithelial squamous lesion and precursor of invasive squamous cell carcinoma (SCC). The 2004 International Society for the Study of Vulvovaginal Disease (ISSVD) classification distinguished two types of VIN: usual type (human papillomavirus (HPV)-related) and differentiated type (not HPV-related). The incidence of usual-type VIN is higher in younger women, while differentiated-type VIN is more common in older patients with chronic dermatologic conditions. Differentiated-type VIN has a greater invasive potential and shorter time between diagnosis and SCC than usual-type VIN. The diagnosis of VIN is carried out by identifying a lesion by visual inspection and confirming by performing a biopsy. Screening tests are not available. Patients with usual-type VIN are at a higher risk of developing another HPV-related malignancy of the anogenital tract; therefore, examination from the cervix to the perianal area is mandatory. The therapeutic approach to VIN balances the invasive potential with the need to be as conservative as possible. Current prophylactic HPV vaccines offer protection against usual-type VIN and related invasive carcinoma.

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Introduction

Health-care providers of women with vulvar dermatological problems include gynecologists, dermatologists, pathologists, primary-care physicians, and nursing personnel, all of whom should be aware of the importance of early diagnosis of vulvar intraepithelial neoplasia (VIN) to minimize the risk of progression to invasive disease and reduce patients’ distress [1].

Classification

The VIN 1–3 grading system adopted in 1986 by the International Society for the Study of Vulvovaginal Disease (ISSVD) represented the first attempt to classify VIN by a scientific body [2]. However, ISSVD abolished this system in 2004. The term VIN is now only used by the ISSVD for high-grade lesions without a grading specification. What was previously VIN 1 is now regarded as a wart or HPV infection and what was VIN 2 and 3 is now simply referred to as VIN [3]. Three diagnostic terms are recommended to classify the pathogenetic type of VIN:

a) VIN, usual type (the most common VIN type, generally related to human papillomavirus (HPV)) (uVIN)
b) VIN, differentiated type (the less common type, generally not related to HPV) (dVIN)
c) VIN, unclassified type (or VIN, not otherwise specified (NOS)) (the occasional example of VIN which cannot be classified into either of the above VIN categories)

Classification is made on the basis of morphologic criteria supported by immunohistochemistry, and it does not involve HPV DNA testing.

Two other pathological classification/grading systems are in use. The World Health Organization (WHO) still grades uVIN into three grades [4]. Recently, the Lower Anogenital Squamous Terminology (LAST) Committee published their terminology. They grade all HPV-associated lesions across the entire lower anogenital tract into two grades: LSIL (low-grade squamous intraepithelial lesion, including infections) and HSIL (high-grade squamous intraepithelial lesion) [5].

Epidemiology

A significantly higher incidence of VIN is reported among white women than among black, Asian/Pacific Islander, or Hispanic women [6]. In the last 30 years, the incidence of VIN has increased and the mean age of diagnosis has decreased: the highest peak is reported during ages 40–49 years and a second smaller peak occurred in women older than 55 [7,8,9]. The age-adjusted incidence of VIN in the period 1997–2004 reported from Surveillance, Epidemiology, and End Results (SEER) databases was 5.0 per 100,000 women [10].

In the majority of VIN, HPV DNA is found and the increase of VIN and vulvar squamous cell carcinoma (SCC) among younger women can be considered as an HPV-associated malignancy [11]. The most recent multicentric study on HPV genotype distribution in VIN and vulvar cancer found HPV DNA in 86.7% of the 587 VIN and 28.6% of 1709 vulvar carcinomas examined. Of the cases of VIN, 91.6% had a single infection and the three most common types of HPV were HPV 16 (77.3%), 33 (10.6%), and 18 (2.5%) [12].

By histological classification, in a series of 1893 cases of VIN, van de Nieuwenhof and coworkers found 96.5% uVIN (median age 47.8 years) and 3.5% dVIN type (median age 67.0 years). From 1992 to 2005, the incidence of uVIN almost doubled (from 1.2/100,000 to 2.1/100,000) and the incidence of dVIN increased ninefold (from 0.013/100,000 to 0.121/100,000). For uVIN, the increase in age has increased the risk of subsequent diagnosis of SCC (2.7% <29 years; 8.5% >75 years) and shortened the time between diagnosis of uVIN and SCC (50 months for the <29-year group and 25 months for the >75-year group). The overall percentage of dVIN patients subsequently diagnosed with vulvar SCC was 32.8% with a median time from dVIN to SCC of 22.8 months [8].

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Vulvar oncogenesis

Epidemiological data confirm two different pathways for vulvar SCC analogous to the two types of VIN: one related to HPV infection and one independent [6,9,10,13,14,15,16]. HPV-related SCC has a mean age of 63.3 years and it is usually warty-basaloid in type, while HPV-independent SCC has a mean age of 70.2 years and it is usually of the keratinizing type. Although the majority of vulvar SCC is not HPV associated, dVIN accounts for only 2–10% of all reported VIN. The possible explanations for dVIN’s low prevalence are that it is a transient lesion that rapidly progresses to invasive carcinoma and/or it is an underdiagnosed and underreported lesion [17,18].

In the HPV type, failure of the immune system to produce an effective response to high-risk HPV is related to virus persistence and host factors (Fig. 1) [19]. The longer the infection persists, the longer the viral oncoproteins E6 and E7 can interfere with important control mechanisms of the cell cycle ultimately leading to escape from programmed cell death and transformation [13,14,20,21,22].

Vulvar oncogenesis independent from HPV infection has proven to be more difficult to study, but appears related to chronic oxidative genetic damages (Fig. 2). p53 and phosphatase and tensin homolog (PTEN) mutations and microsatellite instability have been demonstrated in early-stage HPV-independent vulvar carcinogenesis [16,23,24,25,26]. In addition, the possible role of Ras-association domain family 2A (RASSF2A), O-6-methylguanine-DNA methyltransferase (MGMT), and thrombospondin-1 (TSP-1) genes in transcriptional silence caused by methylation has been reported [27,28].

Clinical aspects

VIN diagnosis occurs during visual assessment of the vulvar region when the patient presents with symptoms or during routine gynecological examination in asymptomatic women, in particular with abnormal pap smear or positive HPV cervical test.

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An appropriate examination of the vulva requires complete exposure and good lighting. It is performed with the naked eye. A magnifying lens or colposcope can be used to enlarge and delineate a previous evidenced area on naked eye examination. Routine application of acetic acid is discouraged as acetowhitrining alone is not specific on the vulva.

The clinical aspects of VIN should be described using general principles of dermatology [29]. VIN has variable features: site (anywhere on the vulva), number of lesions (unifocal or multifocal), size (from a few millimeters to many centimeters), shape (round, oval, or irregular), color (any shade from white to red, or if pigmented, from pale tan to black), and degree of thickness (from scarcely perceptible to warty lesions).

In uVIN, lesions can be multifocal, located around the introitus, often involving the labia minora. They are usually elevated lesions. The surrounding skin/mucosa is usually normal and lesions are sharply defined although they may have irregular or serpiginous outline.

A decreased immune response to HPV infection is associated with multifocality (more than one lesion on the vulva) and multicentricity (involvement of vagina, cervix, and/or anus as well as the vulva) [30,31,32]. Usually, the same type of HPV is involved in all the lesions [31]. Younger patients have a higher risk of multifocal lesions (59% in women aged 20–34 and 10% in patients >50 years of age) [33], but older patients have more often intraepithelial lesions at uncommon sites (vagina, anus, and periurethral region) [34]. A model is constructed in a recent paper where a positive history for anal penetrative sex, immunosuppression, and VIN has a predictive probability of anal intraepithelial neoplasia of 71.8% [35].

The changes of dVIN are less specific than uVIN. dVIN is suspected when treatment-resistant, poorly demarcated pink or white (hyperkeratotic) plaques are seen in women with lichen sclerosis or lichen planus with a long-lasting history of itching and other local symptoms such as soreness, pain, burning, dyspareunia, dryness, or bleeding. The dVIN lesions are sometimes difficult to distinguish from the associated dermatosis. Lichen sclerosis often affects the adjacent skin, and biopsy may not be easy to perform. When such treatment-resistant plaques are biopsied, only a minority will show dVIN. The others will show lichen sclerosis plus lichen simplex chronicus or lichen sclerosis with acanthosis and altered differentiation. Previous, concomitant, or subsequent intraepithelial neoplasia of the cervix, vagina, and anus is rare in patients with dVIN compared to uVIN (2.9% vs. 41.2%) [8].

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Biopsy is the most important step in defining the therapeutic approach for affected patients. In most cases, a single biopsy for lesion is enough to give to pathologist a representative sample of the lesion. In a recent paper, Nugent reported 23% of patients presenting with SCC already present at the time of the initial VIN diagnosis [32], a percentage higher than previous studies [36, 37, 38]. The diagnosis of VIN based on punch biopsy may not be representative of the entire lesion, and the risk of underdiagnosis, that is, that VIN may harbor an occult invasive carcinoma, must also be taken into account.

**Histopathology**

The essential histological feature of VIN is a proliferation of atypical basal cells. The criteria for atypia are as follows: basal layer involvement, enlarged nuclei, hyperchromatic, pleomorphic, and increased numbers of mitotic figures. All five criteria must be present. Atypical mitoses are very suspicious for the diagnosis of VIN, but they are not required for its diagnosis. In addition to atypia, VIN is associated with architectural changes of hyper- or parakeratosis, acanthosis, and a dermal lymphocytic infiltrate.

1. **VIN, usual type.**

In uVIN, the proliferation of atypical basaloid cells begins in the basal layer and involves partial to full thickness of the squamous epithelium. The term “basaloid” is used for cells resembling basal cells, with a small amount of basophilic cytoplasm. Low-power examination of uVIN shows a basophilic appearance due to crowded cells with large, dark nuclei and a small amount of basophilic cytoplasm. Mitoses including atypical mitoses and apoptotic bodies are common throughout the atypical basaloid cell proliferation. Towards the surface, the atypical basaloid cells may mature and they develop abundant, eosinophilic cytoplasm of mature squamous cells. These more mature squamous cells may show a type of HPV-associated cytopathic change termed “koilocytosis.” The criteria for koilocytosis are as follows: squamous cells of the superficial layers that have developed enlarged, hyperchromatic, very irregular, often geometric or “raisinoid” nuclei, perinuclear clear haloes, and dense eosinophilia of the peripheral cytoplasm. Multinucleation and corps ronds are also common features.

**Subtyping uVIN.**

Two subtypes of uVIN are described: warty and basaloid. While there are other associated features, essentially warty VIN shows koilocytosis and basaloid VIN consists only of atypical basaloid cells [39].

However, subtyping VIN is not usually performed for three reasons: 1) both types of VIN are premalignant and treated similarly, 2) an intermediate form (warty-basaloid VIN) is common, and 3) subclassification has not been shown to be reproducible.

2. **VIN, differentiated type**

The key features of dVIN are basal nuclear atypia and premature maturation above the basal layer. The nuclear atypia of the basal layer is subtle, and it is usually the associated features that first draw the attention of the pathologist to the lesion [40]. However, to avoid the inclusion of nonneoplastic diseases within the spectrum of dVIN, the presence of basal nuclear atypia is essential. All the features of atypia (enlarged, hyperchromatic and irregular nuclei, and increased mitoses) must be seen. The prematurely matured epithelium shows marked eosinophilia of the cytoplasm, prominent but reduced numbers of intercellular prickles, large vesicular nuclei, and prominent nucleoli. Intraductal squamous pearls may be seen and portend imminent invasion. The acanthosis may include quite irregular and/or very elongated rete ridges. Frequently, one or more small nests of atypical squamous cells are seen in the superficial dermis. These nests are rounded and similar cytologically to the epidermal squamous cells, and do not show a local change in the stroma or inflammatory reaction. They do not signify invasion. The dermal collagen is always abnormal, either fibrotic or homogenized.
Most commonly, there is fibrosis and the dermal homogenization of lichen sclerosis that may be seen elsewhere in the specimen is lost beneath the differentiated VIN.

In difficult cases, classification of the VIN type may be aided by p53 and p16 immunohistochemistry. Although there are exceptions, the p53+ p16− phenotype supports dVIN, and p53− p16+ supports uVIN [41]. The main difference between condyloma and uVIN is in the degree of atypia, which is much less in condyloma compared to VIN [42]. A negative or nonspecific p16 supports wart as a false negative p16 is very rare in VIN [5]. No doubt, the biggest problem in the differential diagnosis of dVIN is lichen sclerosus. The progression of lichen sclerosus to SCC is a biological continuum (lichen sclerosus, lichen sclerosus plus lichen simplex, dVIN, and SCC) [43] with gradual changes that represent a difficult area of pathology. Basal layer changes are difficult to distinguish from atypia. p53 expression is often of little help as lichen sclerosus plus lichen simplex often shows basal cell positivity in the same pattern as differentiated VIN [44]. When the pathologist cannot decide whether a lesion has crossed the line between lichen sclerosus and differentiated VIN, a close clinicopathological relationship is essential in managing the patient.

**Treatment**

The therapy of VIN is usually dictated by 1) characteristics of the lesion (size, configuration, location, multifocality, and multicentricity), 2) characteristics of the patient (age, general condition, symptomatology, associated disease, psychologic issues, work environment, and reliability to follow up), and 3) available resources and medical skills [45].

The ideal treatment should completely destroy the lesion, improve symptoms, exclude invasion, alter morphology as little as possible, preserve vulvar function, and avoid recurrences. To date, no treatment achieves these goals, and high morbidity and recurrences associated with surgical interventions make it necessary to evaluate the formal evidence available on less invasive but effective interventions for VIN [46].

The two types of VIN share the necessity of close posttreatment follow-up [47], as the risk of progression in treated patients is 4.2% in the largest single institution series [48].

Follow-up is usually 3-monthly during the first 2–3 years after therapy, and when the risk of recurrence is greater, then, in the absence of symptoms or lesions 6-monthly. Cervical cytology or HPV DNA screening with reflex cytology should be repeated annually because of the high risk of multicentric intraepithelial neoplasia in uVIN patients [31]. The duration and frequency of follow-up may potentially impact progression rates, symptomatology, and quality of life (QOL).

Although all women are at risk, older women, particularly postmenopausal, are at a higher risk of SCC at diagnosis and during follow-up [32].

1. **VIN, usual type**

The increasing incidence of uVIN in younger patients and the lower progression rate in this population tend to indicate a conservative management, since extensive surgeries may affect the body image and can be associated with psychosexual problems.

VIN therapy must be individualized. As differences among series can be huge, it is often difficult to compare them and determine the recommended treatment.

**Surgical procedures**

Local excision, consisting of removal of all visible lesions, can be performed with different techniques: scalpel, electrosurgery, or laser. No substantial differences have been reported; all techniques seem to have a similar efficacy [48,49].

a. **Cold Knife surgery**

Surgery is still considered the treatment of choice. Recent works demonstrated that positive margins do not predict the development of invasive disease, so extensive surgeries do not guarantee a cure.
Surgeons should try to be as conservative as possible, taking into account that we can change the QOL of these patients [1]. A 5-mm peripheral margin is appropriate for the management of VIN, though there are no definitive studies evaluating the safety margins in resections [40]. The resection depth is also important: in pilous areas, atypical cells can compromise skin appendages and ideally the whole pilosebaceous complex should be resected. A resection of up to 4 mm is recommended [51]. In hairless areas, the resection depth does not need to exceed 1 mm, since sebaceous glands do not exceed that depth. Optimal esthetic and functional perineo-vulvar reconstruction is now considered as an integral part of treatment of these lesions.

Recurrence rates after excision range from 20% to 40% [52]. In a retrospective study, 46% of the patients with positive margins presented with recurrence compared to 27% of patients with negative margins [53]. The mean time to recurrence was 22 and 44 months, respectively. The presence of multifocal disease was associated with a higher incidence of recurrence.

b. Loop electrosurgical excision procedure.

Wide local excision can be performed with loop electrosurgical excision procedure (LEEP). Compared with laser CO2 vaporization, it has the advantage that a specimen for histological evaluation can be obtained. Terzakis treated 55 women with histologically confirmed uVIN with a 20% recurrence rate at 48 months of follow-up. [54]

c. Laser CO2

CO2 laser excision yields very good cosmetic and functional results in experienced hands. It is fundamental to recognize the colposcopic surgical stromal planes during the excisional surgery, as described by Reid [55], resecting the lesions up to the third plane (reticular dermis) with a 5-mm safety margin. If the resection is deeper, a scar can remain with poor cosmetic and functional results.

A drawback of CO2 laser vaporization is that there is no surgical specimen for histological evaluation. It is of the utmost importance to perform several biopsies in order to rule out invasion as much as possible. Invasion is most likely to be seen in the thickest part of the lesion where the biopsies should be concentrated. In excised VIN, invasion is usually superficial and surgeons performing laser on VIN should be comforted as lymph node metastases post laser are not described in the literature. Vaporization is performed using the specifications for excision [47,55,56]. It is very useful in mucous areas. The complete response rate for CO2 laser vaporization after treatment is almost 75% in the largest series [48,52,56,57]. The lower recurrence-free survival reported in laser-vaporized lesions may be due to multifocal and multicentric lesions treated with vaporization as multicentric lesions are reported to be more frequent in the multifocal VIN group (32.4% vs. 12.5%) [58].

Medical treatments

Many medical treatments have been attempted to avoid surgery in patients with uVIN lesions. Most studies on medical treatment of uVIN lack an adequate number of subjects, uniform inclusion criteria, comparison groups, and adequate follow-up, so no final conclusions about the therapies proposed can be drawn and further trials to investigate efficacy and safety are needed. To date, no medications are approved by the Food and Drug Administration (FDA) for VIN treatment.

a. Cidofovir

Cidofovir is an acyclic nucleoside analogue with antiviral activity. It may induce the apoptosis of HPV-infected cells. In a pilot study of Tristram, four of the 10 patients treated with cidofovir 1% showed complete response [59]. The side effects included ulceration at the site of the affected mucosa. Pilous areas are refractory to treatment.
b. Photodynamic therapy

Photodynamic therapy (PDT) uses a tumor-localizing photosensitizer, 5-aminolevulinic acid (ALA), in combination with nonthermal light to generate oxygen-induced cell death. In the works of Hill-emanns [60] and Fehr [61], clearance rates ranged from 40% to 60%. Hillemanns [52] showed similar efficacy and recurrences in the PDT group compared to laser vaporization and local excision. Patient selection is essential, and more trials are needed to evaluate efficacy and safety.

c. Imiquimod

Imiquimod is an immune response-modifying drug with antiviral and antitumor activity that induces innate and cell-mediated immunity. In uVIN, imiquimod success depends on an induced immune response to HPV.

A successful immune-therapeutical approach probably requires resetting many parameters in the immune response to HPV [19].

A thin layer of imiquimod 5% cream is applied on the lesion and remains overnight without a cover two or three times a week for a period of 12–16 weeks. In case of severe side effects (intense local inflammatory reaction, itching, burning, and flu-like systemic signs), application could be reduced to once a week or leave a 1-week treatment-free period.

Patients must be monitored for efficacy of treatment, symptoms, and side effects.

In the largest prospective, randomized, double-blinded, and placebo-controlled study [62] with 52 patients, a 35% complete response and 46% partial response was found. After a median follow-up of 7.2 years, VIN recurred in only one of the complete respondents, suggesting that imiquimod is effective in the long term [63].

A meta-analysis of randomized control studies, assessing 104 participants, confirmed these findings [46].

Imiquimod-induced clearance of HPV was associated with normalization of immune cell count in uVIN [64] and a number of preexisting conditions can determine the failure of patients’ responsiveness to immunotherapy [17]. Results of larger, placebo-controlled studies are needed to guarantee efficacy and safety.

Observation

Spontaneous regression is reported for uVIN [48,49] where the age of the patient, clinical presentation, and duration of the lesion are the most important factors influencing regression. Jones et al. reported 14 patients with spontaneously regressing VIN. The patients had a mean age of 19.5, short histories, and pigmented, small, multicentric lesions [48]. Nevertheless, spontaneous regression cannot be predicted and close surveillance is recommended for all patients in which it is used.

Vaccination

The strategy of vaccination using E6 and E7 HPV oncoproteins [65] to treat VIN is attractive. [66,67] However, the costs for the development and research of vaccines are very high and the focus is placed on the studies of vaccines to prevent lower genital tract neoplasia, rather than to treat it.

Special cases

Immunocompromised patients

Immunocompromised women are more likely to have lower genital tract neoplasias, and treatment failure and recurrence are also much more frequent [68,69].

There are no consensus guidelines for the management of VIN in this population. Current treatment strategies are not effective in clearing anogenital HPV infection. They are usually aggressive and, due to
frequent recurrences, they end up being mutilating, thus impacting the patients' QOL. As progression to SCC is more common in this group, surveillance and a strict follow-up of the patient to allow rapid detection of suspicious lesions and subsequent treatment is advised. In a recent paper with short-term follow-up, cidofovir had 51% efficacy in the treatment of VIN in human immunodeficiency virus (HIV)-infected patients [70].

The impact of highly active antiretroviral therapy (HAART) on the progression and treatment outcomes for VIN in HIV patients remains to be determined by long-term cohort studies.

2. VIN, differentiated type

This type of VIN is more likely to be associated with invasive disease, and as a precursor of SCC it should be detected and treated as soon as possible.

Surgical excision constitutes the treatment of choice for dVIN. Resection can be performed with scalpel, LEEP, or laser excision. It is important to obtain a specimen for histological evaluation in order to evaluate stromal invasion. Medical therapies are avoided in dVIN [71].

Prevention

HPV prophylactic vaccination

HPV prophylactic vaccination is effective against uVIN; recently published data showed that in the HPV-naive population the vaccine efficacy against HPV-16- and/or HPV-18-related VIN was 94.9% (95% confidence interval (CI) 68.3–99.9%). In the intention-to-treat population, where the women were previously exposed to HPV, the equivalent efficacy was 75.6% (95% CI 48.5–89.6%) [71]. The reduction of precursor lesions of vulvar cancer can anticipate the reduction rates of vulvar cancer [72].

Future directions

In the next few years, the expected increase in incidence rates for HPV-associated cancers makes it necessary for health programs to increase access to early detection and treatment of uVIN. Eventually, the results of HPV prophylactic vaccination will dramatically reduce the uVIN incidence. The identification of patients with lichen sclerosus or lichen planus and their risk factors for the development of dVIN type will remain a challenge for the foreseeable future.

Summary

There are two distinct types of VIN which differ in prevalence, etiology, clinical presentation, histology, and malignant potential: uVIN related to HPV infection and dVIN due to chronic oxidative genetic damages commonly identified in older women in a context of lichen sclerosus.

dVIN, which is not HPV related, accounts for a small proportion (<2–5%) of all VIN lesions and has a higher risk of progression to invasive cancer than uVIN.

In the majority of uVIN, HPV-16 DNA is found. The failure of the immune system to achieve an effective response against high-risk HPV infection is related to HPV persistence, and interference of viral oncoproteins E6 and E7 with cell cycle control mechanisms leads to transformation.

uVIN tends to be multifocal and sometimes multicentric involving the cervix, vagina, and anus. dVIN is usually unifocal and can be difficult to distinguish from the surrounding dermatosis.

An appropriate examination of the vulva and biopsy, with the aid of immunohistochemistry in difficult cases, is essential for the diagnosis of VIN and its typing.

The therapeutic approach depends on the VIN type, localization, size, and focality; patients' age, symptomatology, associated diseases and psychological issues. Lifelong surveillance after therapy for VIN is of utmost importance since removal of lesions is not a guarantee for invasive cancer prevention.

The broad dissemination of HPV-preventive vaccination will reduce the incidence of uVIN and related invasive vulvar cancer.
Conflict of interest

The authors have no conflict of interest.

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