21 Risk Factors and Classification of Vulvar Intraepithelial Lesions

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21.1 Introduction

Over the last few decades, an increasing trend in the incidence of high-grade preinvasive vulvar lesions, also at a younger age, has been reported [1]. The incidence of invasive vulvar cancer is also on the rise, though less compared to the rise in preinvasive lesions [2]. The Surveillance, Epidemiology, and End Results (SEER) data reported and estimated 6020 new cases in 2017 with an incidence of 2.5 per 100,000 women per year. The number of deaths was 0.5 per 100,000 women per year. Approximately 0.3% of women will be diagnosed with vulvar cancer at some point during their lifetime, based on 2012–2014 data [3].

Though almost 85% of high-grade vulvar intraepithelial neoplasia (VIN) lesions are related to human papilloma virus (HPV), HPV DNA is detectable only in 40% of the invasive cancers [4]. In elderly women, many of the HPV-negative vulvar malignancies are associated with chronic dermatologic conditions such as lichen sclerosus [5].

21.2 Classification of VIN

VIN and vulvar squamous cell carcinoma (VSCC) represent neoplastic changes in the epithelium of the vulva. The causes of VIN and VSCC can be broadly categorized into two categories: (1) HPV-related and (2) non-HPV-related inflammatory skin conditions such as lichen sclerosus. The earlier terminology of vulvar lesions did not distinguish the etiopathogenic pathways [6] nor the different malignant potential of these lesions. Over the years, classification and terminology for VIN have been revised to be able to do so. The latest revision was recommended by the International Society for the Study of Vulvovaginal Disease (ISSVD) in 2015 [7].

21.3 Evolution of Nomenclature

The first description of squamous preinvasive lesions of the vulva was around a century ago.

In 1912, J. T. Bowen, a dermatologist, noted hyperplasia of the epidermis of the vulva with absence of the stratum granulosum along with increased mitoses and clumping of the nuclei. There was no evidence of dermal invasion; however, he did speculate that these lesions may be precancerous [8].

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After a decade, Hudelo et al. coined the term 'erythroplasiform dyskeratosis of the vulvar mucosa' to describe the histological features of Bowen's disease [9].

More such cases were reported in the 1940s with one case being associated with vulvar squamous cell carcinoma highlighting the possibility of progression to malignancy [10].

The term 'carcinoma in situ' (CIS) was proposed by Woodruff et al. in 1958, to reduce the variability in the terminology used to describe the precursor lesions [11].

Based on their observations in 1961 on a relatively large number of carcinomas of the vulva, Abell and Gosling [12] reported that intraepithelial squamous cell carcinoma of the vulva exists in three forms:

- Intraepithelial carcinoma simplex, associated with leukoplakic vulvitis
- Intraepithelial carcinoma of Bowen's type
- Intraepithelial carcinoma of Paget's type

Kaufman in 1965 classified the premalignant lesions of the vulva as Queyrat erythroplasia, bowenoid carcinoma in situ and carcinoma simplex [13].

Some studies reported spontaneous regression of lesions similar to CIS, especially in young pregnant women [14, 15]. This made it evident that there was a difference in the natural history of some lesions.

The term 'intraepithelial neoplasia' was first proposed by Richart in 1967 and subsequently by Crum in 1982. The terminology was instituted initially for lesions of the cervix and, later, the vulva [16].

The term bowenoid papulosis of the genitalia was described by Wade et al. in 1979, with many giving a history of preceding viral infection. These lesions on histopathological examination revealed features of carcinoma in situ and stated that bowenoid papulosis was a new entity whose clinical behaviour was unknown if left untreated [17].

21.4 Role of the International Society for the Study of Vulvovaginal Disease (ISSVD)

A society composed of dermatologists, pathologists, and gynaecologists has contributed significantly in determining the terminology used for vulvar lesions over the years since its inception in 1970.

21.4.1 ISSVD (1976)

In 1976, ISSVD came up with a new terminology with the idea of reducing the confusing array of terms. They proposed the term 'squamous cell carcinoma in situ' and 'hyperplastic dystrophy'. Hyperplastic dystrophy was further qualified as mild, moderate or severe atypia [18].

In 1982, the term 'VIN' was first introduced [19], and the ISSVD adopted it as a general category of intraepithelial squamous neoplasms in 1986.

21.4.2 ISSVD (1986)

The ISSVD subdivided the terminology into the following categories:

- Squamous (may include HPV change):
  - VIN 1—mild atypia
  - VIN 2—moderate atypia
  - VIN 3—severe atypia, carcinoma in situ
- Non-squamous: Paget's disease and melanoma in situ.
- The additional category, 'VIN III, differentiated type', was also introduced to include cases associated with dermatologic conditions such as lichen sclerosus [20].

21.4.3 ISSVD (2004)

Over the ensuing years, it was quite evident that VIN 1, 2 and 3 did not exist on a biological continuum, as

earlier thought. VIN 1 composed of condyloma acuminatum and was associated with low-risk HPV types 6 and 11. It did not carry a risk of progression to invasive lesion. However, VIN 2 and 3 were associated with high-risk HPV types and carried a risk of progression to squamous cell carcinoma.

Inclusion of VIN 1 in the earlier classification led to overdiagnosis and unnecessary interventions in low-grade disease and misunderstanding the HPV effect on vulvar lesions [6].

Considering the difference in risk of progression and prognosis, VIN 1 was dropped, and ISSVD proposed a two-tier classification system in 2004 [21]:

- Usual VIN (uVIN): It includes lesions previously classified as VIN 2 and VIN 3. It is subdivided into warty, basaloid, and mixed types and is associated with HPV infection.
- Differentiated VIN (dVIN): It is associated with dermatologic conditions such as lichen sclerosus, not associated with HPV infection.

21.5 Other Classifications

21.5.1 World Health Organization (WHO) Classification

In 2003 WHO had come up with a similar classification and continued to use the VIN 1 as a small proportion of VIN 1 cases were associated with high-risk HPV [22]. WHO revised this classification in 2014.

21.5.2 Bethesda System-Like Classification (2005)

In 2005, Medeiros et al. [23] proposed a classification scheme similar to the Bethesda system for cervical precursor lesions:

- Low-grade vulvar intraepithelial lesion (LG-VIL) category which encompassed several variants of condyloma
- High-grade VIL category (HG-VIL) which included uVIN and dVIN

21.5.3 Recent Classification Systems

21.5.3.1 Lower Anogenital Squamous Terminology (LAST) 2012

After almost 100 years of evolution, there was some consensus among multiple committees, all supporting the terminology 'squamous intraepithelial lesion' (SIL). The College of American Pathologists (CAP) and American Society for Colposcopy and Cervical Pathology (ASCCP) jointly published the Lower Anogenital Squamous Terminology (LAST) guidelines in 2012 [24], unifying the terminology in consensus with ISSVD. It applied to all HPV lesions involving the cervix, vulva, vagina, anus, perineum and penis, under two headings:

- Low-grade squamous intraepithelial lesion (LSIL), equivalent to uVIN 1
- High-grade squamous intraepithelial lesion (HSIL) encompassing uVIN 2 and uVIN 3

The intraepithelial neoplasia (IN) grade could be included in parentheses, if so desired. The LAST terminology was thought to be more reproducible and biologically relevant compared to the earlier systems; however, it was not applicable to the non-HPV-related lesions. Another fallacy of the LAST terminology was that it reintroduced the concept of VIN 1 as LSIL.

21.5.3.2 The WHO 2014 Classification

WHO accepted the SIL terminology but in addition included dVIN as a separate category [25].

The WHO currently classifies vulvar lesions into two different lesions of the squamous epithelium based on the pathogenesis (HPV-induced or HPV-negative).

Squamous intraepithelial lesion (SIL): SIL includes HPV-associated intraepithelial lesions and is further categorized into LSIL and HSIL similar to cervical and vaginal lesions.

Differentiated VIN (dVIN): dVIN refers to HPV-negative lesions which arise in the context of dermatoses (lichen sclerosus and lichen planus). In contrast to HPV-associated lesions (SIL), severity of dVIN is not graded.

While vulvar LSIL has a high rate of spontaneous remission, HSIL and dVIN have a significant risk of progression to invasive carcinoma. dVIN, though less common than HSIL, progresses faster to invasive carcinoma [26].

21.5.3.3 ISSVD 2015

The rationale for changing the terminology in 2015 by ISSVD was to address two major concerns of the LAST terminology: (1) it did not include dVIN lesions, and (2) it had reintroduced the concept of LSIL corresponding to VIN 1 with a potential increase in overdiagnosis and overtreatment [7].

The ISSVD 2015 recommends the following terms:

- Low-grade squamous intraepithelial lesion of the vulva (vulvar LSIL) which includes external genital warts corresponding to VIN 1 lesions (Fig. 21.1)
- High-grade squamous intraepithelial lesion of the vulva (vulvar HSIL) (Fig. 21.2)
- DVIN: vulvar intraepithelial neoplasia, differentiated

The committee came to a conclusion that a modified form of the WHO 2014 classification would address both the concerns regarding the LAST terminology. The version that was finally adopted by the ISSVD does contain LSIL. However, the word 'neoplasia' is replaced by 'lesion', and in parentheses, it needs to be stated whether the meaning of this term is a flat condyloma or HPV effect. This expresses the approach of the ISSVD that LSIL is not precancerous and does not need to be treated, unless symptomatic.

The term HSIL is used, maintaining in parentheses the previous term of usual VIN. Table 21.1 shows comparison between dVIN and HSIL.

'Vulvar intraepithelial neoplasia differentiated' is the third category, just as in the previous ISSVD terminologies.

This terminology was presented, discussed and accepted by a majority vote at the ISSVD World Congress on 28 July 2015. The ISSVD executive council recommends that the present terminology replace all previous versions of terminology of VIN.

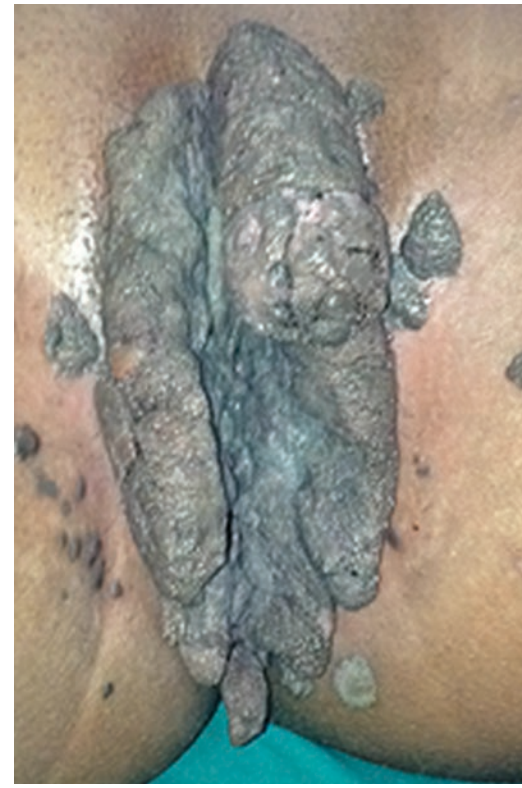

Fig. 21.1 Genital wart. Low-grade squamous intraepithelial lesion

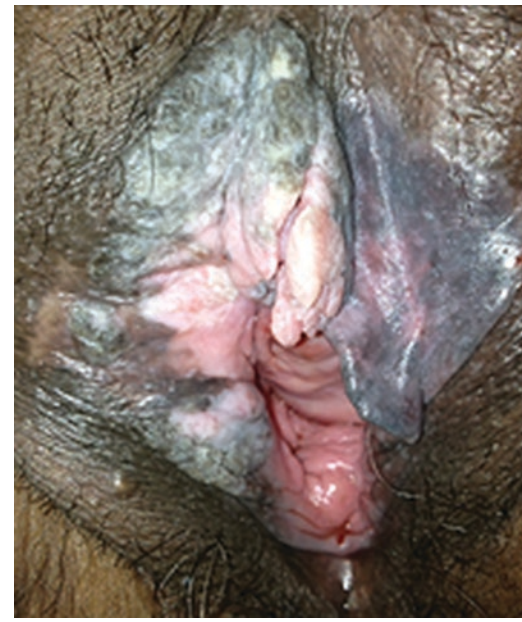

Fig. 21.2 High-grade squamous intraepithelial lesion

Table 21.1 Comparison between dVIN and HSIL[a]

	dVIN	HSIL
Age	Sixth to eighth decade	Third to fifth decade
Percentage of all vulvar preinvasive diagnosis	5	95
Multifocality	Unusual	>50%
Smoking	Not associated	Associated in 60%
Associated conditions	Chronic inflammatory dermatosis, most commonly lichen sclerosus Only 1.5% dVIN HPV+	>80% HPV+
Pigmented clinically	Unknown	10%
Progression to carcinoma	35%	5%
Time from biopsy to invasion	23 months	41 months
Recurrence	Common	less common than dVIN but significant at 15–50%
Immunohistochemistry	Commonly p53+, basal and suprabasal layers	p16 block positivity
Adnexal extension (follicles and sebaceous glands)	Rare	Common
Most common invasion histology if progresses	Keratinizing SCC	Warty/basaloid SCC

dVIN differentiated vulvar intraepithelial neoplasia, *HSIL* high-grade squamous intraepithelial lesion, *SCC* squamous cell carcinoma

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Table 21.2 Evolution of nomenclature for vulvar pre invasive lesions[a]

ISSVD 1976	ISSVD 1986	ISSVD 2004, WHO 2003	Bethesda-like (2005)	LAST 2012 WHO 2014 ISSVD 2015
Mild atypia	VIN I	[b]	LG-VIL – Condyloma – VIN 1	LSIL—VIN 1, condyloma, mild dysplasia, koilocytic atypia
Moderate/severe atypia, CIS	VIN II, VIN III, CIS	uVIN – VIN 2, 3	HG–VIL—VIN 2, 3	HSIL—VIN 2, 3 Moderate/severe dysplasia, CIS
	VIN III, differentiated type	dVIN	dVIN	dVIN[c]

CIS carcinoma in situ, *dVIN* differentiated type VIN, *HG-VIL* high-grade vulvar intraepithelial lesion, *HSIL* high-grade squamous intraepithelial lesion, *ISSVD* International Society for the Study of Vulvovaginal Disease, *LAST* lower anogenital squamous terminology, *LG-VIL* low-grade vulvar intraepithelial lesion, *LSIL* low-grade squamous intraepithelial lesion, *uVIN* usual-type VIN, *VIN* vulvar intraepithelial neoplasia, *WHO* World Health Organization

[a]Reprinted from Pathology, 48(4), Hoang LN, Park KJ, Soslow RA, Murali R, Squamous precursor lesions of the vulva: current classification and diagnostic challenges, Pathology, 291-302, Copyright 2016, with permission from Elsevier

[b]The 2004 ISSVD no longer recognized VIN, but the 2003 WHO retained the designation

[c]dVIN not included in the LAST guidelines

A brief summary stating the various nomenclature classifications is depicted in Table 21.2.

Table 21.3 depicts the latest classification system proposed by the ISSVD 2015.

Table 21.3 Squamous intraepithelial neoplasia—ISSVD 2015 terminology[a]

ISSVD 2015 terminology	Significance	Alias terminology
Low-grade squamous intraepithelial lesion of the vulva	Infection with low-risk HPV causing viral cytopathic effect, atypia in less than or equal to lower third of the vulvar epithelium without cytopathic effect	Flat condyloma Condyloma accuminatum VIN 1 Mild dysplasia
High-grade squamous intraepithelial lesion of the vulva	Premalignant change in more than a third of the epithelium with basaloid/warty appearance, signifies infection with high-risk HPV	Usual VIN, VIN 2, 3 Moderate/severe dysplasia Intraepithelial carcinoma, Bowen type
Differentiated VIN	Premalignant change often associated with an inflammatory dermatosis (e.g. lichen sclerosus), rather than HPV, more aggressive than high-grade squamous intraepithelial lesion	Simplex-type VIN Intraepithelial carcinoma, simplex type Squamous cell hyperplasia with atypia

HPV human papilloma virus, *VIN* vulvar intraepithelial neoplasia
[a]Data from [7]

21.6 Risk Factors for Vulvar Intraepithelial Lesions

Women with vulvar dermatological problems visit various healthcare professionals such as gynaecologists, dermatologists, primary-care physicians and nursing personnel. With the incidence of VIN on the rise and with a potential to progress to malignancy, early diagnosis of VIN is important.

The incidence of both uVIN and dVIN has increased over the last few decades, while the incidence of VSCC has remained relatively unaltered [1].

21.6.1 Race

The incidence of VIN is reported to be higher among white women compared to black, Asian/Pacific Islander or Hispanic women [27].

21.6.2 Age

VIN, usual type, is regarded as a disease of primarily younger women, 3rd to 5th decade of life. Several studies report that the mean age of women diagnosed with VIN 3 has reduced over the years which coincided with an increased incidence of VIN 3 [28].

There is often a second peak in incidence of VIN in the 60- to 80-year range, which may reflect the peak incidence of differentiated-type VIN. Differentiated VIN comprises less than 5–30% of all VIN [29]. Older women with VIN have a higher risk of progression to malignancy.

21.6.3 Behaviour

The increased incidence of VIN is probably a result of certain behavioural changes such as increased sexual promiscuity, HPV, smoking and improved awareness of the disease [30], which also correlate with presence of intraepithelial lesions in the rest of the lower genital tract such as the cervix and vagina.

21.6.4 Risk Factors for Progression to Invasive Carcinoma

Studies have reported presence of dVIN adjacent to VSCC in approximately 40% of the cases. These findings implied that dVIN was more likely to progress to VSCC than uVIN (32.8% vs. 5.7%) and in a shorter time (22.8 months vs. 41.4 months) than uVIN [31, 32]. A history of prior, synchronous or subsequent VSCC is more

often found in dVIN than uVIN (85.7% vs. 25.7% for uVIN) [30].

dVIN are less prevalent, probably because they are transient and/or underreported or underdiagnosed; however, they carry a higher malignant potential than uVIN.

Risk factors for malignant progression in uVIN included advanced age, radiotherapy and immunocompromised status [33].

Human papilloma virus and VIN: Prior to the understanding of the role of HPV as the causative agent of cervical carcinoma, multiple etiological agents were implicated such as herpes simplex virus (HSV), arsenic and even granulomas [11].

Subsequently research revealed that HPV was found to be responsible for the vast majority of anogenital squamous carcinomas and was also detected in VIN [34, 35].

HPV infection is strongly associated with uVIN. Many studies have reported a HPV positivity of >80% [36–38].

HPV16 was the most common type (77.2%), followed by HPV33 (10.6%) and HPV18 (2.6%). Over 90% of LSIL were attributed to low-risk HPV types 6 and 11 [39].

The rate of positivity of high-risk HPV in uVIN is disproportionately higher than that seen in vulvar squamous cell carcinoma. In a study of 1709 VSCC, only 28.6% of cases harboured HPV [40]. This discrepancy led investigators to explore alternative HPV-independent pathways to VSCC, leading to the identification of dVIN as a separate oncogenic pathway to VSCC. A cumulative 134 cases of dVIN have been tested for HPV in the literature, of which only 2 (1.5%) were positive [41].

Failure of the immune system to produce an effective response to high-risk HPV is related to virus persistence and host factors such as age, smoking and sexual behaviour. With the persistence of high-risk HPV infection, viral oncoproteins E6 and E7 can interfere with important control mechanisms of the cell cycle leading to malignancy.

Immunization with the quadrivalent or 9-valent human papillomavirus vaccine, which is effective against human papillomavirus genotypes, has been shown to decrease the risk of vulvar high-grade squamous intraepithelial lesion (HSIL) (VIN usual type) [42].

21.6.5 Smoking and VIN

It has been found that there is a strong association between cigarette smoking and various neoplasms, including vulvar intraepithelial neoplasia. These women present with VIN at a younger age. The percentage of cigarette smokers within the study cohort was similar to that of cervical cancer [43] and had multicentric disease. Smokers are more likely to have microinvasion at the first excision and were not cured in a single session, needing multiple sessions of therapy [44]. Women who continued to smoke after treatment were 30 times more likely to have persistent vulvar disease. A complete assessment of these cases should include proctoscopy in addition to the colposcopic examination of the cervix and vagina [44].

21.6.6 Immunosuppression

Immunosuppression has been reported to increase the incidence of intraepithelial lesions and also the risk of progression to invasive disease. Therefore, the need for follow-up is heightened among these women.

- Iatrogenic immunosuppression: Women who have had renal transplants have been shown to be up to 40 times more at risk of vaginal or vulvar cancers and more likely to develop genital tract dysplasia [45].
- Chronic steroid use with autoimmune disorders and post chemotherapy is also associated with increased incidence of VIN [46].
- Human immunodeficiency virus (HIV): A meta-analysis of 50,000 women with human immunodeficiency virus (HIV) reported a relative risk for VIN of 4.6 and 5.8 for invasive cancer of the vulva and vagina, respectively [47].

HIV-positive women frequently present at a younger age with multifocal and multicentric disease. Close surveillance of the lower genital tract is mandatory to enable early recognition and treatment of any suspicious lesions. Close follow-up after treatment of VIN is essential to exclude early recurrence or progression [48].

21.6.7 Chronic Dermatologic Conditions

- Lichen sclerosus (LS): Lichen sclerosus (LS) is a chronic non-neoplastic, non-infectious, inflammatory skin disorder with a predilection for the genital area with a chronic relapsing remitting course. The condition is currently considered as an autoimmune disorder occurring in genetically predisposed patients. LS predisposes to infections such as candidiasis, herpes or HPV-related lesions due to long-term usage of topical steroids.
  LS is frequently seen in association with dVIN. Long-term studies have shown that LS has 1–3% of progression to VSCC [49, 50] (Fig. 21.3).
  LS has been referred to as atypical LS when there is basal nuclear atypia. Atypical LS may show increased p53 staining and may represent a very early form of dVIN [31].
  LS with hyperplasia, dyskeratosis and parakeratosis, referred to as hypertrophic LS, may or may not have increased risk of progression to VSCC [51].
  It has been proposed that dVIN can develop from lichen sclerosus and that the presence of both strongly increases the cancer risk, especially in women >70 years of age. Women with lichen sclerosus with concurrent VIN had a 10-year VSCC risk of 18% compared with 3% in lichen sclerosus women without VIN [52].
  As a supporting observation, several authors have found both dVIN and lichen sclerosus adjacent to VSCC in 25–65% of the cancer cases [53]. dVIN should be suspected if there is any circumscribed lesion resistant to ultrapotent topical corticosteroids.

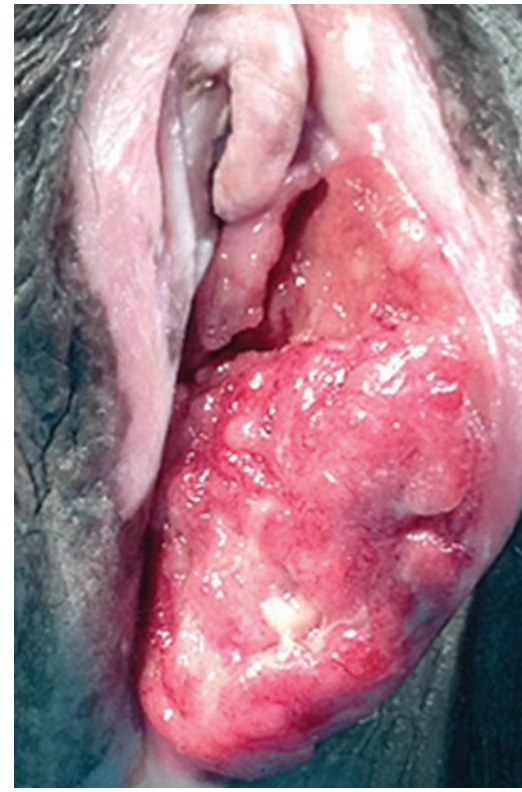

Fig. 21.3 Vulvar squamous cell carcinoma with a backdrop of lichen sclerosus

  Further studies with long-term follow-up are needed to clarify the natural history of LS, atypical LS and hypertrophic LS.
- Lichen planus (LP): Vulvar LP is a chronic condition, with an unpredictable relapsing and remitting course. Transformation into squamous cell carcinoma is rare but documented, especially with erosive LP. It is likely that LP, like LS, has a precursor stage which is resistant to steroids (differentiated VIN, acanthotic LP or usual VIN) before progressing into malignancy [54].

21.6.8 Other Preinvasive Conditions

21.6.8.1 Vulvar Paget's Disease (VPD)

The World Health Organization (WHO) defines VPD as 'an intraepithelial neoplasm of epithelial origin expressing apocrine or eccrine glandular-

like features and characterized by distinctive large cells with prominent cytoplasm, referred to as Paget cells'. It is further classified as primary (cutaneous) and secondary (non-cutaneous) VPD [55].

Primary (cutaneous) VPD:

- Type 1a: Intraepithelial lesion without dermal invasion
- Type 1b: Dermal invasion of Paget's cells
- Type 1c: Cutaneous vulvar disease as a manifestation of an underlying vulvar adenocarcinoma

Secondary (non-cutaneous VPD):

- Type 2: VPD originates from rectal or anal adenocarcinoma
- Type 3: VPD originates from urogenital neoplasia

In approximately 25% of the cases, VPD is invasive; in these cases, the prognosis is worse than in non-invasive cases. Recurrence rates in invasive VPD are high, 33% in cases with clear margins, and even higher when surgical margins are not clear, regardless of invasion.

21.6.8.2 Melanoma In Situ

Melanoma in situ is an uncommon pigmented nonepithelial vulvar preinvasive lesion. The lesion may be clinically similar to more common benign pigmented lesions such as melanosis. Biopsy is a must for diagnosis. The risk of progression to malignancy is unknown, though documented [56]. The in situ phase may extend over a long period of time.

21.7 Conclusion

The incidence of high-grade preinvasive disease of the vulva is increasing and that too in the younger age group. Majority of VIN is associated with HPV infection though in elderly women many of the vulvar malignancies are HPV-negative and are associated with chronic dermatologic conditions. The common risk factors for VIN are persistent high-risk HPV infection, smoking, immunosuppression, promiscuous sexual behaviour and presence of chronic dermatologic conditions such as lichen sclerosus and lichen planus. A high index of suspicion for VIN in women with these risk factors can help in diagnosing the disease early.

Key Points

- Increasing trend in the incidence of high-grade preinvasive vulvar lesions at a younger age has been reported with a relatively stable incidence of invasive cancer.
- The terminology for vulvar epithelial lesions has been modified many times over the years. The present recommended terminology is the one proposed by ISSVD in 2015.
- VIN has dual oncogenic pathways: HPV-related and non-HPV-related, reflected in the present classification systems as LSIL, HSIL for HPV-related lesions and dVIN for non-HPV-related lesions.
- dVIN, though less common, has a higher risk of progression to malignancy, especially with advanced age.
- The common risk factors for VIN are persistent high-risk HPV infection, smoking, immunosuppression, promiscuous sexual behaviour and presence of chronic dermatologic conditions such as lichen sclerosus and lichen planus.
- Non-squamous intraepithelial lesions are extramammary Paget's disease and melanoma in situ.

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