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REVIEW

Squamous precursor lesions of the vulva: current classification and diagnostic challenges

LIEN N. HOANG[1], KAY J. PARK[1], ROBERT A. SOSLOW[1] AND RAJMOHAN MURALI[1,2]

[1]*Department of Pathology, and* [2]*Marie-Josee and Henry R. Kravis Center for Molecular Oncology, Memorial Sloan Kettering Cancer Center, New York, NY, USA*

Summary

Growing evidence has established two major types of vulvar intraepithelial neoplasia (VIN), which correspond to two distinct oncogenic pathways to vulvar squamous cell carcinoma (VSCC). While the incidence of VSCC has remained relatively stable over the last three decades, the incidence of VIN has increased. VIN of usual type (uVIN) is human papillomavirus (HPV)-driven, affects younger women and is a multicentric disease. In contrast, VIN of differentiated type (dVIN) occurs in post-menopausal women and develops independent of HPV infection. dVIN often arises in a background of lichen sclerosus and chronic inflammatory dermatoses. Although isolated dVIN is significantly less common than uVIN, dVIN bears a greater risk for malignant transformation to VSCC and progresses over a shorter time interval. On histological examination, uVIN displays conspicuous architectural and cytological abnormalities, while the morphological features that characterise dVIN are much more subtle and raise a wide differential diagnosis. On the molecular level, dVIN is characterised by a higher number of somatic mutations, particularly in *TP53*. Here we review the classification, epidemiology, clinical features, histomorphology, ancillary markers and molecular genetics of both types of VIN, and discuss the morphological challenges faced by pathologists in interpreting these lesions.

Key words: Diagnosis; pathology; precursor; squamous carcinoma *in situ*; squamous intraepithelial lesion; squamous dysplasia; vulva; vulvar intraepithelial neoplasia.

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INTRODUCTION

Squamous cell carcinomas account for 83% of all malignancies in the vulva.[1] Although the incidence of vulvar squamous cell carcinoma (VSCC) has remained relatively stable over the last three decades, the incidence of vulvar intraepithelial neoplasia (VIN), the putative precursor lesion to VSCC, has increased over time.[2,3] There are two distinct aetiopathogenic pathways leading to VSCC, associated with either: (1) VIN of usual type (uVIN) which is human papillomavirus (HPV)-driven, or (2) VIN of differentiated type (dVIN) which develops independently of HPV. The major features characterising these oncogenic pathways are summarised in Fig. 1.

EVOLUTION OF NOMENCLATURE AND CURRENT CLASSIFICATION

Squamous precursor lesions of the vulva were first recognised a century ago, and since the initial description, numerous terms and classification schemes have been proposed (Table 1).[4–6]

Bowen's disease was first described by the dermatologist J. T. Bowen in 1912. He noted extreme hyperplasia of the epidermis, absence of the stratum granulosum, and numerous mitoses as well as clumping and crowding of the nuclei. At the time, Bowen denied the features of 'distinct carcinomatous formation' due to the absence of dermal invasion, but did speculate on the premalignant nature of the lesions.[7] In 1922, Hudelo *et al.* were the first to recognise the histological features of Bowen's disease in the vulva and termed the disease 'erythroplasiform dyskeratosis of the vulvar mucosa'.[5,8] Twenty years later, Knight reported six cases of Bowen's disease of the vulva, of which one was associated with VSCC. In a review of the literature, he identified an additional 26 cases.[9]

In 1958, Woodruff and Hildebrant recognised the variability in terminology used to describe squamous precursor lesions of the vulva and proposed a unifying term 'carcinoma *in situ*' (CIS).[10] Several groups then noticed that a proportion of lesions that were morphologically identical to CIS demonstrated spontaneous regression, particularly in young, pregnant patients with multicentric disease.[5,11,12] In order to distinguish these lesions from those which progressed to invasive carcinoma, Wade, Kopf and Ackerman in 1979 coined the term 'Bowenoid papulosis'.[13]

In 1961, Abell and Gosling reviewed 150 VSCC and reported two types of squamous precursor lesions: (1) intraepithelial carcinoma of Bowen's type, and (2) intraepithelial carcinoma of simplex type.[14] In 1977, the term 'differentiated' was used to highlight the highly differentiated histological features of the simplex type.[6]

The 1976 International Society for the Study of Vulvovaginal Disease (ISSVD) endorsed the term 'squamous cell carcinoma *in situ*' and 'hyperplastic dystrophy'. The latter was further qualified by mild, moderate or severe atypia. The initial appeal of this change in terminology was that it would replace the confusing array of terms in use at the time, including Bowen disease, erythroplasia of Queyrat, carcinoma simplex, squamous cell hyperplasia with atypia, atypical squamous dystrophy and leukoplakic vulvitis.[15]

The term 'intraepithelial neoplasia' was first proposed by Richart in 1967 and subsequently by Crum in 1982, initially

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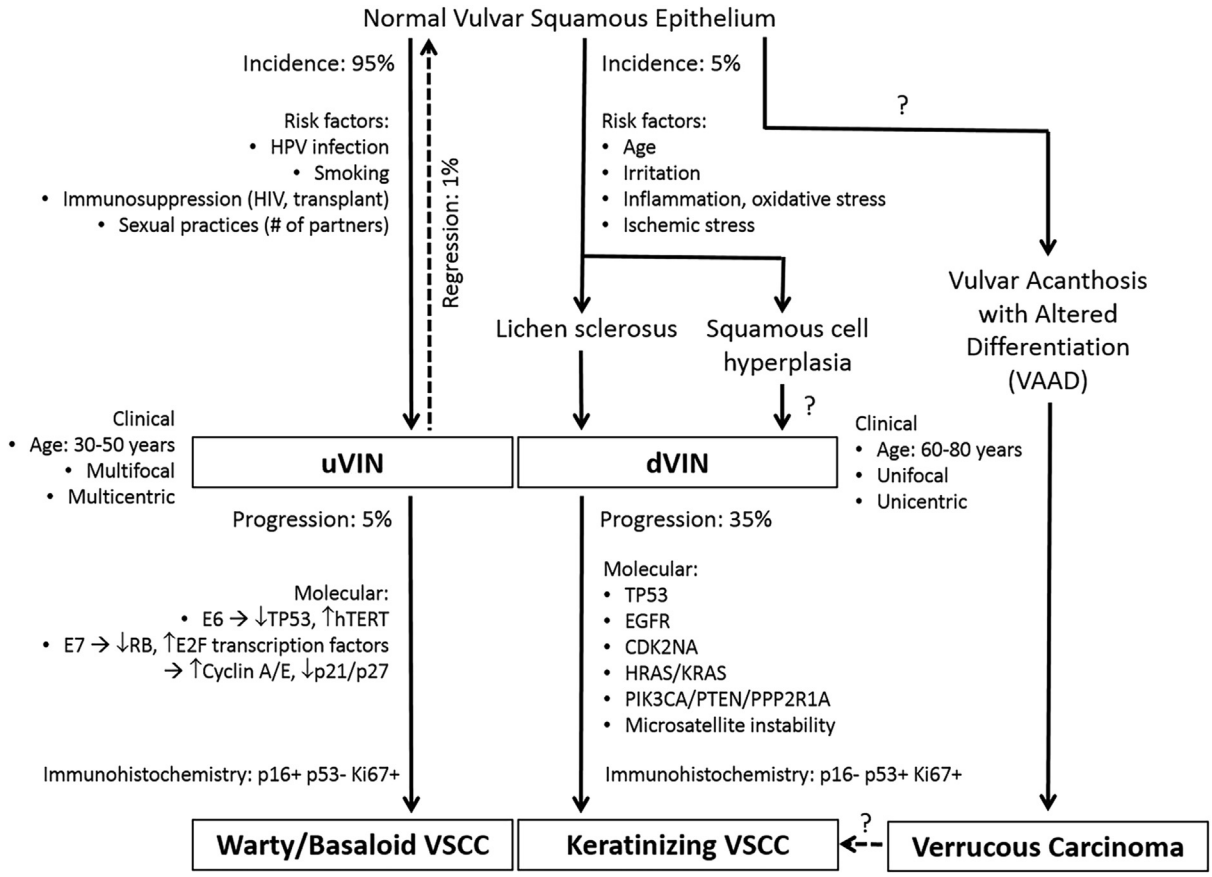

Fig. 1 Pathways of oncogenesis in vulvar squamous cell carcinoma. Modified from Nascimento *et al.*[114]

Table 1 Major classification schemes proposed for squamous precursor lesions of the vulva over time.

1958	1976 ISSVD	1986 ISSVD	2004 ISSVD[a] 2003 WHO[a]	2005 Bethesda-like	2012 LAST 2014 WHO 2015 ISSVD
CIS	Mild atypia	VIN I	–[a]	LG-VIL • Condyloma • VIN 1	LSIL • VIN 1 • Condyloma • Mild dysplasia • Koilocytic atypia
	Moderate atypia Severe atypia or CIS	VIN II VIN III, severe atypia or VIN III, CIS	uVIN • VIN 2 • VIN 3	HG-VIL • VIN 2–3 • dVIN	HSIL • VIN 2–3 • Moderate/severe dysplasia • Bowen disease • Bowenoid dysplasia • CIS
–	–	VIN III, differentiated type	dVIN		dVIN[b]

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] The 2004 ISSVD no longer recognised VIN 1 but the 2003 WHO retained the designation.
[b] dVIN not included in the LAST guidelines.

for lesions of the cervix and later, the vulva.[16,17] In 1986, the ISSVD adopted the term VIN which was graded as VIN I, II and III. By definition, the dysplasia was confined to the lower one-third of the epithelial thickness in VIN I, to the lower two-thirds in VIN II, and involved two-thirds of the epithelial thickness or more in VIN III. The additional category, 'VIN III, differentiated type' was also introduced.[18]

Over the ensuing years, evidence accrued showing that VIN 1, 2 and 3 did not exist on a biological continuum, as the classification implied. VIN 1 consisted almost entirely of condyloma acuminatum and was associated with low-risk HPV types 6 and 11. In contrast, VIN 2 and 3 were associated with high-risk HPV types and carried a risk of progression to VSCC.[5,19] Recognising the aetiological and