ORIGINAL ARTICLES

Squamous Vulvar Intraepithelial Neoplasia

2004 Modified Terminology, ISSVD Vulvar Oncology Subcommittee

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In the current classification, squamous vulvar intraepithelial neoplasia (VIN) is categorized as VIN 1, 2 and 3 according to the degree of abnormality. There is neither evidence that the VIN 1–3 morphologic spectrum reflects a biologic continuum nor that VIN 1 is a cancer precursor. The VIN 2 and 3 category includes 2 types of lesion, which differ in morphology, biology and clinical features. VIN, usual type (warty, basaloid and mixed), is HPV related in most cases. Invasive squamous carcinomas of warty or basaloid type is associated with VIN, usual type. VIN, differentiated type, is seen particularly in older women with lichen sclerosus and/or squamous cell hyperplasia in some cases. Neither VIN, differentiated type, nor associated keratinizing squamous cell carcinoma is HPV related. The term VIN *should apply only to histologically high grade squamous lesions (former terms,* VIN 2 *and* VIN 3 *and differentiated VIN 3). The term* VIN 1 *will no longer be used. Two categories should describe squamous VIN:* VIN, usual type *(encompassing former VIN 2 and 3 of warty, basaloid and mixed types) and* VIN, differentiated type *(VIN 3, differentiated type).* (J Reprod Med 2005;50:807–810)

Classification is performed on the basis of morphologic criteria only and not HPV type or clinical appearance.

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Historical Background

The current terminology for squamous vulvar intraepithelial neoplasia (VIN) was introduced by the International Society for the Study of Vulvar Disease (ISSVD) in 1986. In this classification, squamous VIN is categorized as VIN 1, VIN 2 and VIN 3 according to the degree of abnormality. In addition, the 1986 report described a separate lesion, differentiated VIN, and recommended that it also be classified as VIN 3.[1]

In 2003 the World Health Organization (WHO) recommended grading VIN lesions the same as cervical intraepithelial lesions.[2] In this classification, a VIN 1 lesion is defined as follows: "Maturation is present in the upper two-thirds of the epithelium,

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and the superficial cells contain variable but usually mild atypia, which may include viral cytopathic effect (koilocytosis). Nuclear abnormalities are present throughout but are slight. Mitotic figures are present in the basal third and are not numerous. Abnormal forms are rare."[2]

A VIN 2 lesion has cellular maturation "present in the upper half of the epithelium, and nuclear atypia is conspicuous in both the upper and lower epithelial layers. Mitotic figures are generally confined to the basal two-thirds of the epithelium. Abnormal forms may be seen."[2]

A VIN 3 lesion is defined as follows: "Maturation (including surface keratinization) may be absent or confined to the superficial third of the epithelium. Nuclear abnormalities are marked throughout most or all of the thickness of the epithelium. Mitotic figures may be numerous and are found at all levels of the epithelium. Abnormal mitoses are frequent."[2]

The simplex type of VIN (carcinoma in situ, simplex type) is described separately and defined as follows: "a highly differentiated lesion resembling well differentiated squamous cell carcinoma in which the atypia is most prominent in or confined to the basal and parabasal layers of the epithelium, where the cells have abundant cytoplasm and form pearls and the nuclei are relatively uniform in size and contain coarse chromatin and prominent nucleoli." [2]

WHO prefers the VIN terminology but lists dysplasia/carcinoma in situ as synonyms.

Reasons for Modification

The 1986 ISSVD report made no reference to the possible natural history of VIN. Inappropriate parallels have been drawn between cervical intraepithelial neoplasia (CIN) and VIN because they have similar 1–3 grading systems, reaffirmed in the 2003 WHO publication. However, there is no evidence that the VIN 1–3 morphologic spectrum reflects a biologic continuum or that VIN behaves similarly to CIN.

VIN 1 is an uncommon histologic finding and constitutes basally located cellular changes or minimal atypia. These findings are usually reactive or are an HPV effect. There is no evidence that VIN 1 is a cancer precursor, suggesting that the term *intraepithelial neoplasia* for such benign lesions may be misleading. In addition, studies have demonstrated considerable interobserver and intraobserver variations in the VIN 1 diagnosis and concluded that this diagnostic category is not reproducible.[3,4] Finally, certain lesions, usually occurring in a background of lichen sclerosus, have basally located atypia, representing high grade differentiated VIN. It is essential that these be properly identified and managed.

The majority of VIN lesions are categorized as VIN 2 or 3. Good histologic agreement is obtained when VIN 2 and 3 are combined as a single diagnostic category, high grade VIN.[4] However, the high grade VIN category includes 2 types of lesion, which differ in morphology, biology and clinical features.

VIN, usual type, is HPV related in most cases and seen adjacent to approximately 30% of squamous cell carcinomas of the vulva. Invasive squamous carcinomas of warty (condylomatous) and basaloid types have been identified associated with VIN of the usual type, and these tumors are also HPV associated.[2] In women >30 years old, these lesions have a demonstrated invasive potential. While it is relatively common to see invasion developed in a field of VIN,[5,6] a number of factors should be considered in addressing the natural history of VIN, usual type, lesions: unifocality,[7] previous radiotherapy,[8] raised lesions[6] and immune suppression.[8,9] The role of the immune system seems to be central to the processes associated with both progression to invasion and spontaneous regression of VIN. Indirect evidence to support this hypothesis may be found in the high incidence of VIN in immunocompromised women.[10] Adequate follow-up is crucial when we consider the invasive potential of VIN. The progression of untreated VIN, usual type, to invasive carcinoma is clearly demonstrated.

A particular clinical variant of VIN, usual type, with a pigmented appearance and multiple, seen in women <30 years who often are non-European, often associated with genital warts and sometimes with pregnancy, can regress spontaneously.[11]

The less common VIN, differentiated type, is seen primarily in older women, often in association with keratinizing squamous cell carcinomas and, in some cases, is associated with lichen sclerosus and/or squamous cell hyperplasia in some cases.[2,12-15] VIN, differentiated type, was previously referred to as VIN, simplex type.[15]

VIN, differentiated type, is underreported with respect to keratinizing vulvar invasive carcinoma. Some hypothesis could explain the underdiagnosis of differentiated VIN: the likelihood that it has a relatively brief intraepithelial phase before progression to invasive carcinoma, has the clinical aspect of squamous hyperplasia and is a difficult histologic

diagnosis. Thus, differentiated VIN is discovered mainly during follow-up because of a prior invasive vulvar carcinoma or lichen sclerosus.[13]

HPV DNA and histopathologic studies of vulvar carcinoma and adjacent epithelium confirmed 2 separate etiologies of vulvar cancer. HPV-positive warty or basaloid VIN may be found adjacent to corresponding warty (condylomatous) or basaloid carcinoma, although a given tumor may have both warty and basaloid VIN.[16] Conversely, neither VIN, differentiated type, nor associated keratinizing squamous cell carcinoma is associated with HPV.[13] Good interobserver histopathologic reproducibility is noted between these 2 vulvar carcinoma types.[17]

These data suggest dividing VIN (VIN 2 and VIN 3) into 2 histologic diagnostic categories: *VIN, usual type* (VIN 2 and 3, encompassing warty, basaloid and mixed types) and *VIN, differentiated type* (VIN 3, differentiated type). Furthermore, the clinical features of these lesions are also different. VIN, usual type, is typically seen as a unifocal or multifocal lesion with a variety of clinical presentations: patches, erosions, plaques, papules and nodules with hyperkeratotic, verrucous, pigmented, red or white changes. Conversely, VIN, differentiated type, is most commonly encountered in a background of lichen sclerosus, and the lesion is either an ulcer, warty papule or hyperkeratotic plaque.

There are rare reports of VIN 2 and 3 that are pagetoid in type[18] or that cannot be classified into any of the above categories. In these rare instances VIN can be termed *VIN, unclassified.*

VIN Terminology (Figure 1)

1. The term *VIN 1* will no longer be used. Histologic changes previously encompassed within the term *VIN 1* will be described either as flat condyloma acuminatum or HPV effect. In this context, the use of the term *atypia* is discouraged.
2. The term *VIN* should apply only to histologically high grade squamous lesions (former terms, VIN 2, VIN 3 and differentiated VIN 3).
3. Two categories of VIN should be used to describe squamous VIN:
   a. The more common type of VIN will be termed *VIN, usual type.* This encompasses the previous VIN 2, VIN 3 (clinically older terms: Bowen's disease, bowenoid papulosis; histologically older terms: dysplasia, carcinoma in situ and other VIN terms). These lesions are generally associated with high-risk HPV types, especially HPV 16. VIN, usual type, can be subcategorized histologically as warty (condylomatous), basaloid or mixed (presence within the same lesion of warty and basaloid VIN).
   b. The less common type of VIN lesion will be termed *VIN, differentiated type.* These lesions generally are not associated with HPV.
4. The occasional example of VIN that cannot be classified into either of the above VIN categories (usual and differentiated types) may be classified as *VIN, unclassified type* (or *VIN, NOS*). The rare VIN of pagetoid type may be classified as such or placed in this category.
5. Classification is performed on the basis of morphologic criteria only and not HPV type or clinical appearance.

VIN, usual type
- a. VIN, warty type
- b. VIN, basaloid type
- c. VIN, mixed (warty/basaloid) type

VIN, differentiated type

Figure 1 Squamous VIN terminology (ISSVD, 2004). The occasional example of VIN that cannot be classified into either of the above VIN categories (usual or differentiated type) may be classified as *VIN, unclassified type.* The rare VIN of pagetoid type may be classified as such or placed in this category.

References

1. Wilkinson EJ, Kneale B, Lynch PJ: Report of the ISSVD Terminology Committee. J Reprod Med 1986;31:973
2. Wilkinson EJ, Teixeira MR: Epithelial tumours, squamous tumours. *In* World Health Organization Classification of Tumors: Pathology and Genetics: Tumors of the Breast and Female Genital Organs. Edited by FA Tavassoli, P Devilee. Lyon, IARC Press, 2003, pp 230, 316–320
3. van Beurden M, de Craen AJ, de Vet HC, et al: The contribution of MIB 1 in the accurate grading of vulvar intraepithelial neoplasia. J Clin Pathol 1999;52:820–824
4. Preti M, Mezzetti M, Robertson C, et al: Inter-observer variation in histopathological diagnosis and grading of vulvar intraepithelial neoplasia: Results of a European collaborative study. Br J Obstet Gynaecol 2000;107:594–599
5. Husseinzadeh N, Recinto C: Frequency of invasive cancer in surgically excised vulvar lesions with intraepithelial neoplasia (VIN 3). Gynecol Oncol 1999;73:119–120
6. Chafe W, Richards A, Morgan L, et al: Unrecognized inva-

sive carcinoma in vulvar intraepithelial neoplasia (VIN). Gynecol Oncol 1988;31:154–165

7. de Belilovsky C, Lessana-Leibowitch M: Bowen's disease and bowenoid papulosis: Comparative clinical, viral, and disease progression aspects. Contracept Fertil Sex 1993;21: 231–236
8. Jones RW, Rowan DM: Vulvar intraepithelial neoplasia: III. A clinical study of the outcome in 113 cases with relation to the later development of invasive vulvar carcinoma. Obstet Gynecol 1994;84:741–745
9. Friedrich EG Jr, Wilkinson EJ, Fu YS: Carcinoma in situ of the vulva: A continuing challenge. Am J Obstet Gynecol 1980; 136:830–843
10. Ferenczy A, Coutlee F, Franco E, et al: Human papillomavirus and HIV coinfection and the risk of neoplasias of the lower genital tract: A review of recent developments. Can Med Assoc J 2003;169:431–434
11. Jones RW, Rowan DM: Spontaneous regression of vulvar intraepithelial neoplasia 2-3. Obstet Gynecol 2000;96:470–472
12. Kaufman RH: Intraepithelial neoplasia of the vulva. Gynecol Oncol 1995;56:8–21
13. Yang B, Hart WR: Vulvar intraepithelial neoplasia of the simplex (differentiated) type: A clinicopathologic study including analysis of HPV and p53 expression. Am J Surg Pathol 2000;24:429–441
14. Jones RW: Vulval intraepithelial neoplasia: Current perspectives. Eur J Gynaecol Oncol 2001;22:393–402
15. Hart WR: Vulvar intraepithelial neoplasia: Historical aspects and current status. Int J Gynecol Pathol 2001;20:16–30
16. Kurman RJ, Toki T, Schiffman MH: Basaloid and warty carcinomas of the vulva: Distinctive types of squamous cell carcinoma frequently associated with human papillomaviruses. Am J Surg Pathol 1993;17:133–145
17. Trimble CL, Diener-West M, Wilkinson EJ, et al: Reproducibility of the histopathological classification of vulvar squamous carcinoma and intraepithelial neoplasia. J Lower Genital Tract Dis 1999;3:98–103
18. Raju RR, Goldblum JR, Hart WR: Pagetoid squamous cell carcinoma in situ (pagetoid Bowen's Disease) of the external genitalia. Int J Gynecol Pathol 2003;22:127–135