Review Vulval intraepithelial neoplasia: making sense of the literature

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Key content:

- Vulval intraepithelial neoplasia (VIN) encompasses two entities which are distinct clinically and pathologically.
- VIN, usual type, primarily affects younger women; the incidence is rising.
- VIN, differentiated type, is a difficult histological diagnosis and is regarded as a disease of the elderly.
- Both lesions have significant malignant potential.
- Traditionally, management has been surgical, but conservative approaches are becoming increasingly popular.

Learning objectives:

- To be able to identify the differences between types of VIN in terms of epidemiology, clinical features, pathology and natural history.
- To know about the options available for the management of VIN.

Ethical issues:

- In view of the significant malignant potential, should women with VIN be offered conservative treatment?

Keywords human papillomavirus / International Society for the Study of Vulvovaginal Disease classification / surgical excision / topical treatment / vulval carcinoma

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Introduction

In the 1960s, the term cervical intraepithelial neoplasia (CIN) was first introduced, as well as a pathological grading system to categorise premalignant changes of the cervix. It was assumed that precancerous vulval lesions were akin to cervical lesions and so the term vulval intraepithelial neoplasia (VIN) followed.

Vulval intraepithelial neoplasia is distinct from CIN and encompasses two clinical entities, termed VIN, usual type, and VIN, differentiated type. Historically, usual-type VIN has been referred to as classic VIN, Bowen's disease and bowenoid papulosis; differentiated-type VIN has been termed carcinoma in situ of simplex or variant type.

In 1986 the International Society for the Study of Vulvovaginal Disease (ISSVD) devised a classification system for VIN which remains the most commonly used system in the literature. Abnormalities in vulval tissue were categorised as VIN 1–3, depending on the level of dysplasia present, which is similar to the current grading of CIN. It is now widely believed, however, that VIN 1 is not a precursor of VIN 2 or 3 and that it has a low malignant potential, unlike VIN 2 and 3. For these reasons, the ISSVD modified the classification system in 2004 (**Box 1**).[1] VIN, usual type, describes pathology associated with human papillomavirus (HPV) and is further categorised into warty, basaloid and mixed pathological subtypes. VIN, differentiated type, is not associated with HPV, but often with lichen sclerosus and lichen simplex chronicus.[1] Several other grading systems exist, but the ISSVD system is thought to be the most clinically useful.[2] Despite this, many clinicians and pathologists have not adopted the most recent ISSVD terminology.

Although it was first described nearly a century ago, VIN remains shrouded in historical beliefs and unfounded claims. The aim of this review is to outline conclusions that can be drawn from the current literature on VIN.

Epidemiology

Vulval intraepithelial neoplasia is an uncommon condition. VIN, usual type, is regarded as a disease of primarily younger women, mostly in their 30s or 40s. Several studies report that the mean age of women diagnosed with VIN 3 decreased in the last half century,[3] which coincided with an increased incidence of VIN 3. Investigators have explained this as the result of increased sexual promiscuity, HPV, smoking and improved awareness of the disease in clinical practice. No recent data have been published to confirm a continuing rise in the incidence of VIN, usual type. The peak incidence of VIN usually occurs in the 30 to 50-year age group, depending on the population studied, but there is often a second peak in the 60 to 80-year range, which may reflect the peak incidence of differentiated-type VIN[4–6] (which is believed to be a disease of older women, although little evidence for this exists).

Unfortunately, data on the individual incidences of usual-type and differentiated-type VIN lesions are lacking, as most investigators amalgamate these clinical entities. Nonetheless, usual-type VIN, particularly the warty subtype, is believed to account for the majority of cases. For example, a recent UK study by Athavale *et al.*[7] of 69 women with VIN reported that 90% of VIN specimens were of usual type, 6% were of differentiated-type and 4% were unclassifiable. Of the usual-type VIN, most were purely warty lesions.

The proportion of women with VIN who are current smokers has been reported as 32–84%. An even higher number have a history of smoking: in some studies approaching 100%.[8–10] No groups distinguished the frequency of smoking between the two types of VIN, but it is generally believed that cigarette smoking is strongly associated with VIN, usual type. This type, like other forms of lower genital tract carcinoma in situ, is more frequent among immunocompromised women.[11–13] The percentage of women with VIN who are immunosuppressed has been reported as 5%.[7,9]

Pathology

The pathology of usual-type VIN is well documented as easily recognisable carcinoma in situ, although a variety of microscopic appearances have been described. Classically, the epidermis is thickened, keratinocytes appear disorganised, there is a high nuclear:cytoplasmic ratio and nuclear atypia and abnormal mitotic figures may be seen throughout the epidermis (**Figure 1**). Pyknotic nuclei, corps ronds and dyskeratotic cells with dense eosinophilic cytoplasm are often observed.[14,15] In usual-type VIN of warty subtype, the epidermal surface has a papillary configuration; multinucleated cells, koilocytes and dyskeratotic cells are frequently present. In contrast, usual-type VIN of basaloid subtype has a relatively flat surface and the epidermis is replaced by small, less differentiated cells with a high nuclear:cytoplasmic ratio. As the name suggests, usual-type VIN of mixed subtype shares features of both.[8,15]

Box 1
Current classification (ISSVD) of vulval intraepithelial neoplasia

VIN usual type
- warty subtype
- basaloid subtype
- mixed subtype

VIN differentiated type

By contrast, the pathology of differentiated-type VIN has not been well documented. It is a difficult, less robust diagnosis, most easily identified adjacent to an invasive squamous cell carcinoma. The classical features are a thickened epidermis, surface parakeratosis, elongated rete ridges and enlarged keratinocytes with a disordered pattern of maturation (**Figure 2**). There is often little or no apparent atypia above the basal layers.[15,16] Adjuvant diagnostic tools, particularly immunohistochemistry, are becoming increasingly popular as a means of confirming the diagnosis and type of VIN.

Great variability exists among reports in the literature as to the frequency of HPV infection in VIN. Working with the findings of numerous recent studies, one group of investigators calculated that the mean HPV positivity in VIN lesions is 85%.[17] Another study isolated HPV types 16 and 18 in 76% of VIN cases.[18]

Multifocal disease has been documented among 40–100% of women with VIN.[3,9,15] Multicentric disease also appears to be a frequent finding. Other forms of lower genital tract intraepithelial neoplasias and cancers, namely cervical, vaginal and anal, are common.[7–9] It has been reported that multicentric disease occurs in approximately one-third of cases.[3] However, the definition of multicentric disease and the distinction between usual-type and differentiated-type VIN are not always clarified, so the exact frequencies of multifocal and multicentric disease in each type of VIN remain obscure. Studies on the pathology and associated HPV status of differentiated-type VIN suggest that this is a unifocal disease process.[16,17,19]

Clinical presentation

Approximately two-thirds of women with VIN experience pruritus. Pain, ulceration and leukoplakia are less usual presenting symptoms, either alone or in combination with pruritus (**Table 1**). Approximately 20% of women remain asymptomatic, the diagnosis being made incidentally. The labia majora, labia minora and posterior fourchette are commonly affected sites, but a smaller proportion present with lesions of the mons pubis, clitoris and perineal and perianal regions.[3,9]

There is great variability in the appearance of usual-type VIN lesions. Red or white plaques are frequent, but they may appear papular, polypoid, verruciform or pigmented (**Figure 3**). Usual-type VIN is almost always a distinct lesion; differentiated type appears less conspicuous, often with ill-defined, raised areas of greyish white,[15] commonly on the background of lichen sclerosus or lichen planus.[20,21] There is no specific clinical appearance that consistently distinguishes usual-type VIN from differentiated VIN. The appearance of a distinct red or white bump with an ulcerated, eroded or roughened surface suggests invasion.[15]

Unfortunately, the diagnosis of differentiated-type VIN remains challenging. It is frequently overlooked in benign conditions, such as lichen simplex chronicus,[16] and missed because of the subtle pathology.[22]

Natural history

A large systematic review of published patient data[3] reported that 3.2% of suspected VIN lesions confirmed at pathology are associated with an occult vulval carcinoma and a further 3.3% of women with

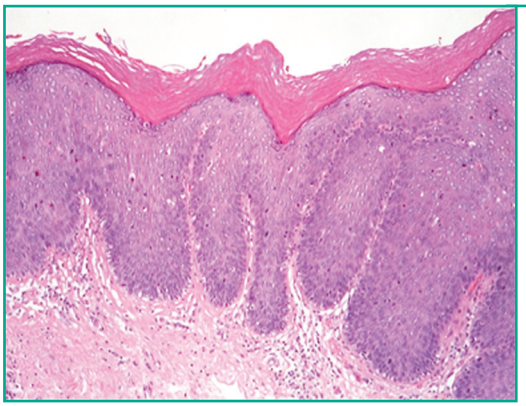

Figure 1
Vulval intraepithelial neoplasia, usual type, is easily recognised by the characteristic pathological features extending across the epithelium

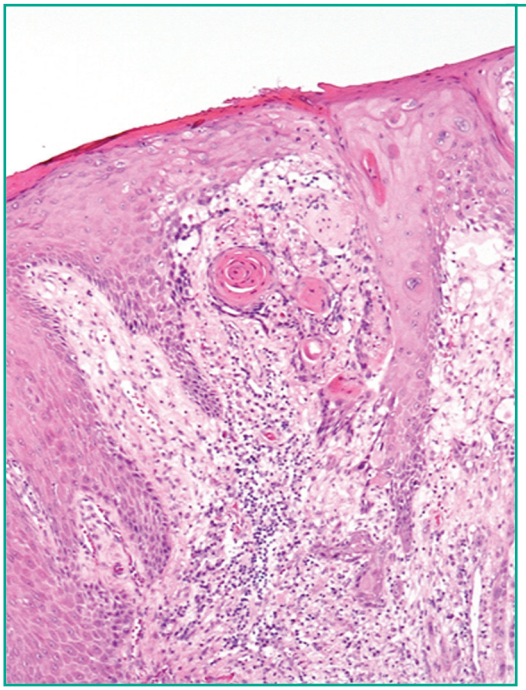

Figure 2
In differentiated-type VIN, the pathological changes are confined to the basal cell layer. An early squamous cell carcinoma is seen in the centre

Presentation	VIN, usual type	VIN, differentiated type
Symptoms	Pruritus Pain Ulceration	Pruritus Burning sensation
Clinical appearance	Highly variable Distinct outline	Ill defined, usually raised area
Associated lesions	Cervical/vaginal/anal intraepithelial neoplasia	Lichen sclerosus Lichen planus

Table 1
Comparison of the clinical presentation of usual type and differentiated-type VIN[3,9,15,21]

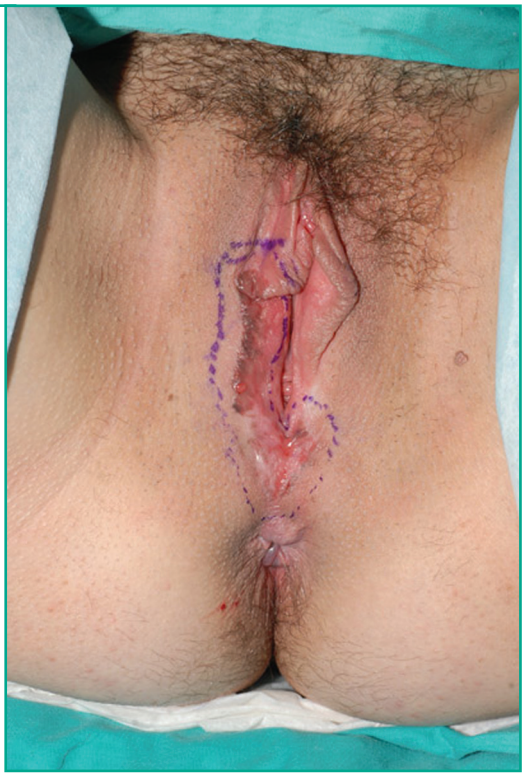

Figure 3
Wide local excision of VIN, usual type (the abnormal area is outlined in pen)

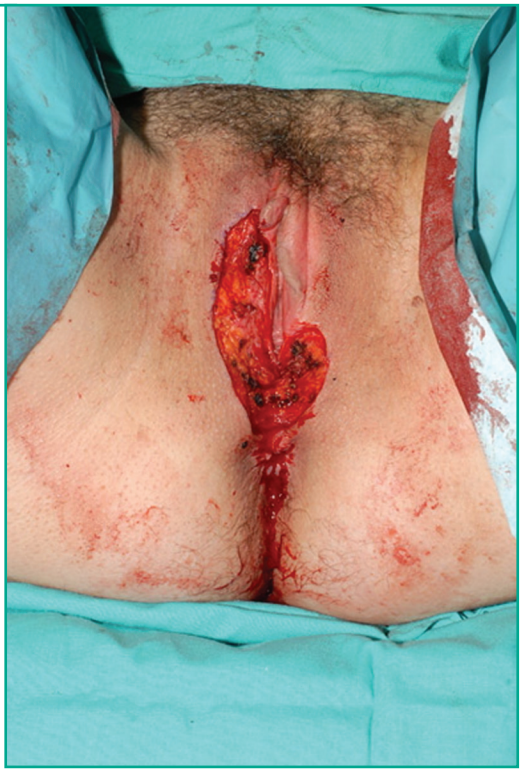

Figure 4
Wide local excision of VIN, usual type (the area outlined in pen in Figure 3 has been excised)

VIN lesions diagnosed after surgical excision develop invasive disease. Other clinicians and pathologists have reported higher rates of underlying invasion in newly diagnosed VIN. For example, MacLean[23] highlighted numerous studies where occult carcinomas were discovered in 15–22% of cases. In the systematic review,[3] spontaneous regression was reported in approximately 1%. Regression was associated with a younger age, multifocal disease and pregnancy. In 9% of untreated cases VIN progressed to invasive carcinoma. Much higher rates of progression have been reported; for example, Jones and Rowan[24] reported a rate of progression of 90% if left untreated, compared with 4% if excised. Considering the frequency of usual-type VIN compared with differentiated type, the majority of women in these studies were likely to have VIN of usual type, but the results are only truly applicable to VIN in general as the authors did not make the distinction. It is recognised that differentiated-type VIN has a high malignant potential, but this has never been reliably quantified.[16,21,22]

Management

The ideal treatment for VIN should:

- exclude invasive disease
- relieve symptoms
- eradicate HPV infection
- minimise distortion of adjacent tissues
- reduce risk of progression to invasive disease
- sustain remission.

Unfortunately, no treatment exists to date that satisfies these criteria.[25]

In the UK, surgery remains the standard management of VIN.[26] Historically, radical surgical procedures such as complete or partial vulvectomy were often carried out.[17] A large study[3] which evaluated various treatments found no difference in rates of recurrence of VIN or progression to invasive disease after vulvectomy, partial vulvectomy, local excision or laser vaporisation procedures; free surgical margins did not reduce the risk of progression. This supports the general consensus that local excision with the aim of completely excising the lesion (**Figure 4**) is the best surgical method for treating VIN, as it limits iatrogenic morbidity.

Surgery can be mutilating, particularly in usual-type VIN, where lesions are often multifocal. Disorders of body image, sexual dysfunction and loss of libido are commonly experienced after surgical procedures.[27] Increasingly, plastic and reconstructive techniques are being applied after surgical procedures to limit subsequent psychological and sexual morbidity by re-establishing normal vulval anatomy and minimising functional losses. It has been proposed that V-Y, labial and Limberg flaps are most appropriate following local excision. An alternative to a flap is a full-thickness skin graft (**Figure 5**).[28]

Laser vaporisation is a destructive procedure which does not allow for biopsy to be obtained; laser excision is a similar procedure but it allows for pathological evaluation of the excised specimen. In both cases, healing is by second intention, but a low thermal effect is said to produce excellent cosmetic

results.[21] Few studies have described the results of laser vaporisation in the treatment of VIN and fewer still have evaluated laser excision. Both of the two small relevant studies[29,30] found laser excision to be superior to laser vaporisation in curing VIN. Laser therapies may be carried out as outpatient procedures using local anaesthesia. In more extensive disease, numerous sessions may be required and treatment can be painful. Laser excision requires a high degree of skill and experience.[21]

Topical treatments are an attractive option because they preserve normal anatomy and sexual function better than traditional surgical interventions. Various topical therapies have, therefore, been studied in small cohorts and have shown mixed results.

Topical imiquimod, an immune-response modifier, is established as an effective treatment for genital warts.[20] Over the last decade it has been tried as a therapeutic option in VIN with varied success and the results of several phase 2 trials have been published. In a recently published double-blind randomised controlled trial[31] aiming to determine the efficacy of imiquimod in the management of VIN, 26 women received imiquimod cream and a further 26 received placebo, both twice weekly over a 4-month period. Lesion size decreased in all but five cases in the intervention group compared with none in the placebo group. In 8 of the 26 women treated with topical imiquimod, the original lesion disappeared, as confirmed by pathological examination. Despite thus confirming the high efficacy of topical imiquimod cream in the management of usual-type VIN, the study also highlighted the adverse effects of imiquimod therapy, namely vulval pruritus and pain, experienced by 24 of the 26 women. Others have reported similar findings.

Photodynamic therapy, topical 5-fluorouracil, corticosteroids, cidofovir, retinoids, dinitrochlorobenzene and interferon alfa have all been tried in small studies but, in all cases, either the results were poor, the supporting data were inconclusive or adverse effects limited clinical use.[25]

Prophylactic vaccines against HPV have been found to be highly immunogenic, with few adverse effects.[32] Large studies assessing the efficacy of quadrivalent vaccines (against HPV types 6, 11, 16 and 18) report seroconversion in approximately 98% of individuals, antibody titres raised for at least 5 years and prevention of warts, VIN and vaginal and vulval carcinoma in the intervention groups. The initiation of the national HPV vaccination programme for teenage girls in the UK should result in a striking reduction in the incidence of HPV-induced vulval diseases; it has been estimated that two out of three intraepithelial lesions of the lower genital tract and half of vulval carcinomas among younger women will be prevented by implementation of the programme.[18] Limited data also suggest that vaccinations may prove effective in the treatment of established usual-type VIN.[33]

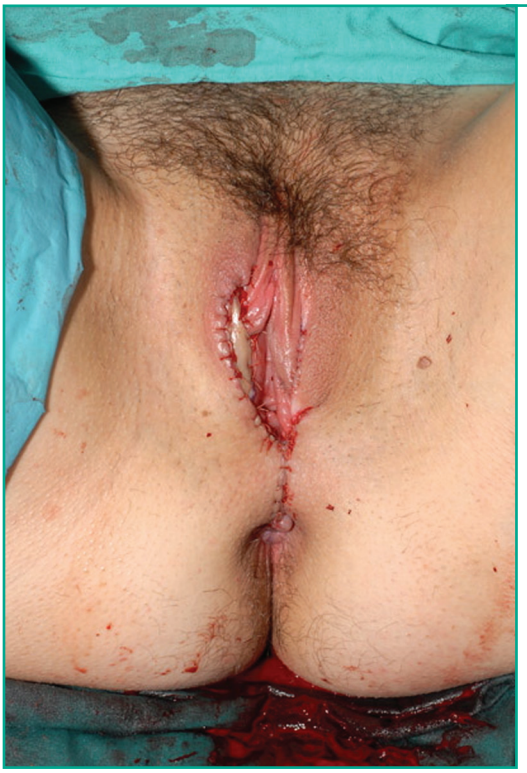

Figure 5
Wide local excision of VIN, usual type, followed by a combination of primary closure and a full-thickness skin graft

It is important to note that studies on the management of VIN have assessed treatment methods mostly in usual-type VIN. Little evidence exists for the use of therapies in differentiated-type VIN. Surgical excision has been advocated as the treatment of choice for differentiated-type VIN.[21] Considering that HPV is not implicated in the pathogenesis of differentiated-type VIN, antiviral therapies and vaccination are unlikely to be successful preventive or treatment strategies.[16]

Conclusion

Despite advances in the medical management of VIN, surgical excision remains the treatment of choice in the majority of centres.[25] Considering the risk of occult carcinoma at presentation, conservative management could prove detrimental. Nevertheless, in women with recurrent disease, topical therapies are an attractive alternative to further surgery. When VIN is multifocal and/or multicentric, complete surgical excision is a challenging task and information gained at biopsy is invaluable. Laser excision appears promising but larger studies are required to confirm whether or not it is an effective treatment option.

Over the next few decades there are likely to be striking changes in the epidemiology of VIN in the UK. With the recent implementation of a national HPV vaccination programme aimed at preventing

cervical carcinoma, a decrease in the incidence of HPV-associated VIN may be expected. Since the UK population is increasingly elderly, VIN in the older group may become a more prominent clinical entity. Over the last 10 years there have been advances in our understanding of VIN, but much further research is required to improve our knowledge of premalignant vulval disease.

Recommended website

International Society for the Study of Vulvovaginal Disease [www.issvd.org/]

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