Premalignant and malignant squamous lesions of the vulva

Maureen L Harmon

Abstract

Vulvar premalignant squamous lesions include low- and high-grade intraepithelial neoplasias. High-grade lesions include classic (usual) and differentiated (simplex) vulvar intraepithelial neoplasia (VIN). Classic VIN (cVIN), the most common, is related to human papilloma virus (HPV), occurs in younger patients, and is frequently multifocal. Differentiated VIN (dVIN), less common, is related to lichen sclerosus and other chronic vulvar dermatoses, occurs in older women, and is usually unifocal. Terminology schemes for premalignant lesions are reviewed. Invasive squamous cell carcinoma also occurs in two distinct clinicopathologic settings. Most conventional keratinizing squamous cell carcinomas arise from a background of dVIN and comprise the majority of invasive squamous tumours. Warty and basaloid invasive squamous cell carcinomas likely develop from cVIN and comprise a minority of invasive tumours. Clinical features, microscopic findings, differential diagnoses, immunoprofile, prognosis and treatment of premalignant and malignant lesions are addressed.

Keywords classic; condyloma acuminatum; differentiated; HPV; human papilloma virus; lichen sclerosus; simplex; squamous cell carcinoma; VIN; vulva; vulvar intraepithelial neoplasia

Introduction

The premalignant squamous lesion of the vulva is designated as squamous dysplasia. The majority of vulvar dysplasias are associated with human papilloma virus (HPV) infection and are referred to as "classic" vulvar intraepithelial neoplasia (cVIN). A separate intraepithelial neoplastic proliferation with a pathogenesis unrelated to HPV, which is related to lichen sclerosus and other vulvar dermatoses is designated as "simplex" or "differentiated" VIN (dVIN). Although condyloma acuminatum (CA) is not a true premalignant lesion, like classic VIN it is HPV-associated and is considered by some to be a low-grade lesion, hence its inclusion in this review. Although carcinoma of the vulva is the fourth most common gynaecologic malignancy, it is relatively rare, accounting for only 5% of all female genital tract cancers. Over 90% of invasive vulvar tumours are squamous cell carcinomas.

The most frequent form of invasive squamous cell carcinomas (invSCC) of the vulva, conventional keratinizing squamous cell carcinoma, occurs in elderly women and is related to dVIN, lichen sclerosus (LS) and probably other dystrophic vulvar lesions including squamous hyperplasia. The less common forms of invSCC, the warty and basaloid subtypes, account for one-third of vulvar invSCC, are seen in relatively young women, are associated with HPV and are preceded by cVIN.

Over the last decade much new information has shed light on the pathogenesis of vulvar precursor lesions and invSCC, leading to considerable changes in terminology for both. Therefore, before turning our attention to the individual precursor lesions, a discussion of terminology is warranted.

Terminology

Currently there are four grading systems in place, reflecting the heterogeneity of vulvar precursor lesions, and taken as whole may be complicated and confusing for the novice as well as the experienced pathologist. There are two separate grading systems utilizing the (VIN) terminology and two systems using the two-tiered cytology-based squamous intraepithelial lesion (SIL) terminology known as the Bethesda System.

The VIN terminology, adopted in 1986, is a three-tiered system and was devised to replace the atypia-carcinoma-in-situ terminology. It is the most widely accepted nomenclature system and was, until recently, endorsed by both the World Health Organization (WHO) and the International Society for the Study of Vulvovaginal Disease (ISSVD). This system recognizes three grades of VIN: I, II, and III, where VIN I is defined as a low-grade lesion and VIN II and III are high-grade lesions. VIN II/III encompasses lesions previously classified as carcinoma in situ, Bowen disease, and bowenoid papulosis. This system is analogous to the cervical intraepithelial neoplasia (CIN) terminology which is widely utilized for cervical precursor lesions. In addition, the VIN system also recognizes differentiated or simplex VIN, which by definition is a high-grade lesion.

In 2004, ISSVD proposed a novel VIN nomenclature, a complete revision that has not been universally accepted. Essentially, the revised system eliminates the VIN I category and combines VIN II and III into a single category (Table 1). Thus, grading of VIN is eliminated. Instead, VIN is separated into two groups: classic (undifferentiated or usual) and differentiated (simplex) types. The classic type includes the WHO VIN categories II and III. The classic type is further subdivided into warty, basaloid, and mixed (warty and basaloid) types. VIN I is excluded because it is deemed poorly reproducible, uncommon, and may mimic reactive changes from inflammation or differentiated VIN.[1,2] Because of high inter-observer variability, VIN II and III cannot reliably be separated and should be placed in the same category. ISSVD also noted that the occasional example of VIN that cannot be placed into either of the two VIN categories (classic nor differentiated type) may be classified as "VIN, unclassified type".

The squamous intraepithelial lesion (SIL) system for grading vulvar precursor lesions is based on the Bethesda System, which has been used for years in the reporting of cervical cytology and biopsies. The Bethesda System is two-tiered and divides dysplasia into low-grade SIL and high-grade SIL. While the VIN systems do not include condyloma acuminatum as VIN I, the SIL terminology places condyloma in the LSIL category. Finally, in 2005 Medeiros et al proposed yet another grading system based

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Classification systems for VIN

ISSVD 1986/WHO	ISSVD 2004	Bethesda	Bethesda-like
VIN I	Flat condyloma HPV effect	LSIL	LGVILs
VIN II, III	1. VIN, usual type a. VIN, warty type b. VIN, basaloid type c. VIN, mixed (warty/basaloid) type	HSIL	HGVILS
Differentiated VIN	2. VIN, differentiated type		

Table 1

on the Bethesda System which utilizes the terms low- and high-grade vulvar intraepithelial lesions, LGVIL and HGVIL and has been called the Bethesda-like system.[3]

At our institution, we report vulvar biopsies using both the VIN and SIL terminologies. For example, low-grade lesions are reported as LSIL (VIN I) and high-grade lesions as either HSIL (VIN II) or HSIL (VIN III).

Condyloma acuminatum

Introduction

Condyloma acuminatum (CA) is a sexually transmitted benign squamoproliferative lesion caused by HPV, most frequently types 6 and 11. Because it is not associated with high-risk HPV subtypes, it is not a cancer precursor lesion.

Clinical features

CA occurs in approximately 1% of sexually active reproductive age females, usually in the early years of sexual activity. The lesion most frequently involves the external genitalia, including the vulva, introitus, perineal, and perianal skin and less frequently the vagina and cervix. CA is usually asymptomatic but may cause vulvar itching and burning. The clinical correlate to condyloma is the genital wart. Grossly, the lesion is exophytic, usually multiple, and can range in size from minute raised lesions to large cauliflower-like coalescing masses. CA has a tendency to recur, especially in immune-compromised patients. Although not life-threatening, the cosmetic and social issues relating to these lesions are not insignificant and likely influenced the decision to include HPV types 6 and 11 in the quadrivalent (6, 11, 16, 18) HPV vaccine.

Microscopic findings

The classic condyloma has an exophytic branching, papillary growth pattern with stratified squamous epithelium and underlying fibrous stroma. There may be overlying parakeratosis and hyperkeratosis (Figure 1). Koilocytic atypia, which can range from subtle to conspicuous, is seen in surface layers of the infected epithelium. Koilocytic atypia includes nuclear enlargement and coarsening, nuclear membrane irregularity, binucleate forms, and perinuclear cytoplasmic halos. When mitotic figures are present, they are confined to the lower third of the epithelium.

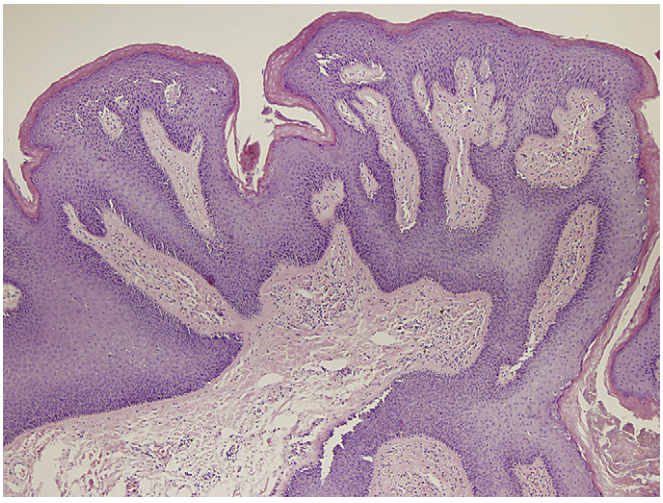

Figure 1 Condyloma acuminatum with characteristic exophytic, papillary architecture (H & E, original magnification 4×).

Differential diagnosis

Various lesions with verrucous-like squamous proliferations can be mistaken for CA. A frequent mimic is the benign fibroepithelial polyp. The distinction between the two lesions can be particularly challenging when the condyloma shows only very subtle koilocytic change. However, the fibroepithelial polyp, unlike condyloma, demonstrates atypical multinucleated stromal cells. Another frequent mimicker of condyloma is vulvar seborrhoeic keratosis (VSK) which is also a discrete lesion. VSK, in contrast to CA, consists of a proliferation of basaloid cells and usually contains horn pseudocysts (Figure 2). However, the distinction between the two may prove to be irrelevant as a recent study demonstrated HPV positivity in the majority of VSKs in contrast to cutaneous seborrhoeic keratoses which were almost exclusively HPV negative.[4] Thus, VSKs may represent an altered phenotype of CA. Finally, CA needs to be distinguished from various forms of VIN, most importantly the warty subtype of high-grade VIN. The high-grade lesion shows marked nuclear

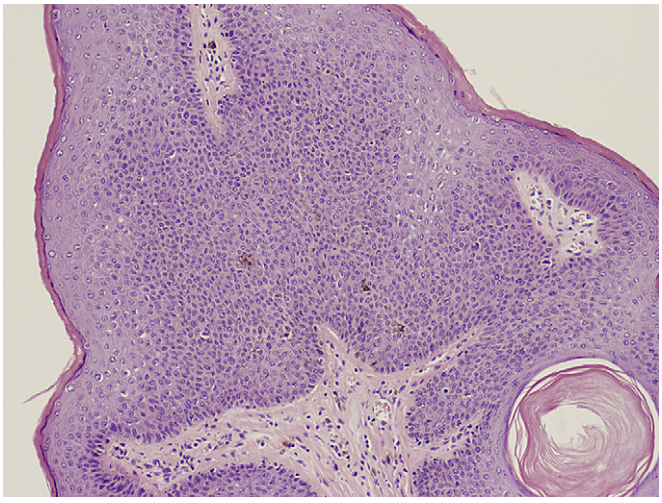

Figure 2 Proliferation of basaloid cells and a horn pseudocyst in vulvar seborrhoeic keratosis (H & E, original magnification 10×).